Handbook

of *nutrition, diet and sleep*

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Summary points

- The sleep-wake cycle is comprised of three different states of alertness: wakefulness, non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep.
- Physiologic processes and most organ systems demonstrate changes across states of alertness.
- Most nuclei involved in the sleep-wake circuitry can be classified as either wake-promoting or sleep-promoting.
- Hypocretin-producing neurons located in the posterior hypothalamus innervate the ascending arousal system to promote wakefulness.
- The ventral lateral preoptic area located in the anterior hypothalamus innervates the ascending arousal system to promote sleep.
- Nuclei involved in REM sleep regulation can be classified as REM-on or REM-off neurons. These nuclei mutually inhibit each other to regulate transitions from NREM to REM sleep.
- A two-process model composed of a circadian process and homeostatic process synchronizes the sleep-wake cycle to the 24-hr day.
- The advent of the polysomnogram (PSG) has allowed us to define sleep stages based upon brain waves: stage wake, stage N1, stage N2, stage N3, and REM sleep.
- Sleep architecture changes across the human lifespan.
- Sleep disorders, medical, and psychiatric diseases may lead to cortical arousals, sub-cortical activations, and alterations in cyclic alternating patterns.

1. Neurologic basis of sleep: an overview

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Abstract

Over the last century significant advances in technology and science have provided us with a better understanding of the regulation and control of the sleep-wake cycle. Characterization of normal sleep and wakefulness has naturally led to the identification and classification of normal variants and a myriad of sleep disorders. Recent discoveries have begun to uncover the intricate relationships between nutrition, diet, and sleep. This chapter provides a very basic review of sleep-wake regulation, states of alertness, and physiologic correlates to lay the foundation in sleep medicine for which the reader will build upon as they delve into subsequent chapters.

Keywords: NREM sleep, REM sleep, wake, electroencephalogram, polysomnogram

Abbreviations

AASM	American academy of sleep medicine
CAPS	Cyclic alternating patterns
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
GABA	Gamma-amino butyric acid
LDT/PPT	Laterodorsal and pedunculopontine tegmental nuclei
NREM sleep	Non-rapid eye movement sleep
PSG	Polysomnogram
REM sleep	Rapid eye movement sleep
RLS	Restless leg syndrome
SCN	Suprachiasmatic nuclei
SLD	Sublaterodorsal nucleus
SWS	Slow wave sleep
vlPAG/LPT	Ventral part of the periaqueductal gray /lateral pontine tegmentum
VLPO	Ventral lateral preoptic area
WASO	Wake after sleep onset

1.1 Introduction

Theories about sleep and wakefulness date back to ancient Greece when people attributed the control of sleep to Hypnos, the god of sleep. In the early 20th century, von Economo proposed that the hypothalamus was the 'center for regulation of sleep'. The advent of the EEG and the PSG in the last century provided researchers with a foundation for which to study sleep. These technologies led to the discovery of three different states of being: wakefulness, NREM, and REM sleep. Different sleep stages were defined and associated with dynamic changes in physiologic processes and organ systems. Recent findings have shown that control of the sleep-wake cycle, in addition to the hypothalamus, depends upon central nervous system structures including the brainstem and the basal forebrain. Theories have been proposed and tested to help explain how these processes are entrained to the 24-hr day to yield a stable sleep-wake cycle. The characterization of the normal sleep-wake circadian rhythm has led to descriptions of abnormal sleep-wake cycles and, ultimately, the description of the myriad number of sleep disorders (AASM, 2005). Epidemiologic studies have shown that sleep disorders can lead to increased mortality and morbidity. Recent findings suggest that disorders producing hypoxemia and sleep fragmentation may cause generalized oxidative stress leading to altered cellular metabolism with diffuse inflammatory changes. This may, in turn, lead to the increased morbidity and mortality. The effects of the epidemic of obesity, sedentary lifestyles, and societal pressures placed upon the sleep-wake cycle make the *Handbook of nutrition, diet, and sleep* a timely publication that will hopefully foster more research across these disciplines and help to educate the healthcare community and the public about how sleep affects all aspects of our being.

1.2 Modern understanding of sleep/wake control

1.2.1 The anterior and posterior hypothalamus

At the turn of the 20th century, Gelineau, Westphal, and von Economo attracted the attention of neurologists as they set the stage for our modern understanding of sleep/wake control. In the latter half of the 19th century, Gelineau and Westphal described individuals that would fall to the floor unintentionally following laughter and fall asleep unintentionally during the daytime in a condition now referred to as narcolepsy-cataplexy (Gélineau, 1880; Westphal, 1877). Baron von Economo, in 1930, postulated that the hypothalamus (what he called the 'interbrain') was the 'center for regulation of sleep' (Von Economo, 1930). This observation came about through his study of those afflicted with 'Spanish' influenza during the pandemic between 1916 through 1928. The infection resulted in many people exhibiting residual neurological signs and symptoms including hypersomnia, insomnia, and Parkinsonism. Through post-mortem studies of these victims, von Economo hypothesized that 'insomnia' resulted from lesions in the anterior part of the hypothalamus while 'hypersomnia' was due to lesions in the posterior part of the hypothalamus. In other words, different parts of the hypothalamus are able to promote sleep and wakefulness and lesions in the hypothalamus can result in long-term sleep disorders.

Further investigations continue to support von Economo's findings that the hypothalamus is instrumental in the sleep-wake process. The VLPO, a sleep-promoting area of the anterior hypothalamus, has been shown to be most active during sleep and least active during wakefulness (Espana and Scammell, 2011). The sleep promoting activity of the VLPO is carried out via the inhibitory neurotransmitter GABA and the inhibitory neuropeptide galanin. On the other hand, the posterior hypothalamus contains excitatory neurons producing hypocretin (also known as orexin) that promote wakefulness via innervations to most arousal regions of the brainstem and cerebral cortex, which is commonly referred to as the ascending arousal system (De Lecea *et al.,* 1998; Espana and Scammell, 2011; Sakurai *et al.,* 1998) (Figure 1.1). The excitatory hypocretin/orexin neurons are most active during wakefulness and silent during sleep (Espana and Scammell, 2011). Interestingly, the syndrome Gelineau and Westphal described in the late 19th century – narcolepsy with cataplexy – was recently found to be due to the loss of hypocretin/orexin (Nishino *et al.,* 2000; Peyron *et al.,* 2000; Thannickal *et al.,* 2000).

1.2.2 States of alertness: wake, NREM sleep, and REM sleep

Up until the middle of the 20th century, science recognized only two normal states of being: wake and sleep. Written explanations and theories concerning sleep date back to the ancient Greeks and, then, in the 19th century, it was suggested that congestion of cerebral vessels led to sleep. Theories about sleep became more scientifically tenable after Hans Berger, in 1928, recorded brain activity using surface electrodes with a newly described instrument, the EEG (Berger, 1930). This eventually led to the discovery of REM during sleep (Aserinsky and Kleitman, 1953). Soon after this discovery of rapid eye movements during sleep, William Dement and others reported that a high incidence of dream recall occurred when subjects were awakened during periods of REM
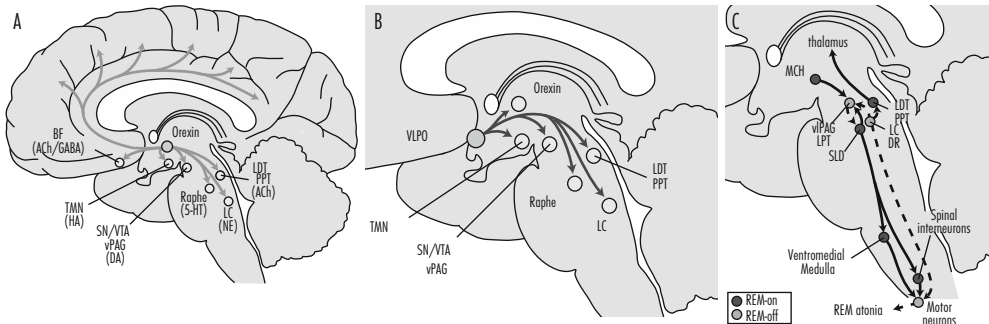
Figure 1.1. Examples of pathways involved in states of wakefulness, non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep. (A) Wakefulness: orexin/hypocretin-producing neurons in the lateral hypothalamus innervate all of the ascending arousal systems as well as the cerebral cortex to promote wakefulness. (B) NREM sleep: the ventrolateral preoptic area (VLPO) neurons are active during NREM sleep. (C) REM sleep: the laterodorsal and pedunculopontine tegmental nuclei (LDT/PPT) and the sublaterodorsal nucleus (SLD) are REM-on neurons. The lateral pontine tegmentum (vlPAG/LPT) and locus coeruleus/dorsal raphe (LC/DR) are REM-off neurons. Solid lines depict pathways active during REM sleep; dashed lines are pathways inactive during REM sleep (from Espana and Scammell, 2011).
BF = basal forebrain; MCH = melanin-concentrating hormone; TMN = tuberomammilary nucleus.

sleep (Dement and Kleitman, 1957). The association of these rapid eye movements with changes in muscle tone and an active EEG pattern resembling wakefulness led to the concept of three different states of being: wakefulness, NREM sleep, and REM sleep (Jouvet *et al.,* 1959).

Researchers then began investigating physiologic functions across these different states of being (Orem and Barnes, 1980). Parasympathetic nervous system activity progressively increases from wakefulness to NREM to REM sleep while the sympathetic nervous system decreases from wakefulness to NREM sleep and then increases with significant fluctuations during REM sleep. Heart rate tends to decrease from wakefulness through NREM sleep but varies during REM sleep. Cerebral blood flow increases during REM sleep. REM sleep leaves the body in a state of almost complete muscle paralysis (muscle atonia), sparring only the extra-ocular muscles, diaphragmatic muscles, and genitalia. Ironically, penile erections and clitoral engorgement occurs during this state of atonia in REM sleep. REM sleep was soon regarded as a state of paradoxical sleep: a state of heightened brain activity – demonstrating an EEG rhythm similar to wakefulness – vivid dreaming, penile erections or clitoral engorgement, all occurring with inhibition of voluntary muscle activity. Similar to the heart rate changes, respiratory rate decreases in NREM sleep but is quite variable in REM sleep. Normal ventilatory changes during sleep lead to a 2-3% decrease in blood oxygen saturation and 2-6 mm Hg increase in partial pressures of carbon dioxide. In addition, hormones (e.g. an increase growth hormone in slow wave sleep) have been shown to fluctuate across these states. Other physiologic functions that decrease in NREM and REM sleep include but are not limited to the following: alveolar ventilation; hypoxic and hypercapnia ventilatory responses; upper airway muscle tone; cardiac output and peripheral

vascular resistance; glomerular filtration rate, which leads to a decrease in urine production; and, decreased swallowing and salivation. Gastric motility decreases during sleep and gastric acid secretion peaks at approximately midnight. In summary, the sleep/wake cycle is a very dynamic process associated with changes in nearly every organ system.

1.2.3 The sleep-wake switch and rapid eye movement-on/off

Hypothalamic regulation of the sleep-wake cycle had already been described dating back to the 1930's but recent research has uncovered other regions of the brain involved in the regulation of the sleep-wake cycle. Monoaminergic, GABAergic, and cholinergic neurotransmission arising from the midbrain and the pons along with other areas of the brain such as the basal forebrain have been shown to contribute to the regulation of the sleep-wake cycle (Espana and Scammell, 2011). In general, the nuclei involved in the sleep-wake cycle can be classified as either sleep or wake promoting. In a simplified model of the sleep-wake cycle, these sleep and wake promoting regions reciprocally inhibit each other when either system fires (Espana and Scammell, 2011; Saper *et al.,* 2001). This leads to a stable sleep-wake switch that resists haphazard changes between states of wakefulness and sleep (Saper *et al.,* 2001).

This general concept of sleep and wake promoting regions of the brain helps explain transitions from sleep to wakefulness, and vice versa, but fails to address how sleep oscillates from periods of REM and non-REM sleep. There also appears to be mutually inhibitory circuits that regulate NREM-REM oscillations similar to the regulation of sleep-wake transitions. Specific cholinergic neurons located in the pons (i.e. LDT/PPT) promote REM sleep, referred to as REM-on cell groups (Espana and Scammell, 2011). Increased cholinergic activity in this region leads to longer and more intense periods of REM sleep (Espana and Scammell, 2011). Another region that has REM-on neurons is the SLD (Espana and Scammell, 2011). These REM-on neurons send projections to the ventral medulla and ultimately spinal motor neurons to produce almost complete muscle atonia. On the other hand, regions that inhibit these REM-active neurons, referred to as REM-off neurons, include the monoaminergic nuclei (e.g. dorsal raphe and locus coeruleus) and the ventral part of the periaqueductal gray to the vlPAG/LPT (Espana and Scammell, 2011). These REM-off neurons inhibit the REM-on neurons leading to the inhibition of REM sleep (Espana and Scammell, 2011). These monoaminergic neurons inhibit the LDT/PPT cholinergic neurons and the vlPAG/LPT inhibits the SLD leading to the inhibition of REM sleep (Espana and Scammell, 2011). Thus, normal regulation of sleep and wakefulness can be viewed as a 'sleep-wake switch' with mutually inhibitory sleep and wake promoting regions as well as REM-on and REM-off regions that regulate NREM/REM oscillations.

The flu epidemic and recent discovery of hypocretin deficiency in narcolepsy and cataplexy demonstrate how small perturbations in this complex circuitry can have dramatic and devastating effects upon the regulation of the sleep-wake cycle. Researchers have now turned to very sophisticated molecular and genetic studies, advanced neuronal labeling techniques, and optogenetic studies in hopes of gaining a better understanding of the complex neural circuitry underlying the three states of alertness: wake, NREM, and REM sleep.

1.2.4 The circadian process and homeostatic process of sleep and wake

This brief and simplified overview of the sleep-wake cycle discussed thus far explains how we transition from wake to sleep and from NREM to REM sleep, and vice versa, but fails to explain how individuals synchronize sleep and wakefulness to the light/dark cycle. In a two-process model of sleep regulation introduced in 1982, there is a circadian (process C) and a homeostatic process (process S) that act together to produce a regular sleep and wake cycle (Borbely, 1982). Humans have a sinusoidal rhythm of approximately 24 hrs that help to regulate behavioral and physiologic processes such as the sleep and wake cycle, thermoregulation, and hormonal release. In mammals, the circadian pacemaker of sleep is located in the anterior hypothalamus, specifically in the SCN (Zee and Manthena, 2007). This endogenous, rhythm-producing clock is not completely self-sufficient and isolated from the external environment. It is governed (entrained) by external stimuli known as zeitgebers with the strongest stimulus being light. As light enters the eye it stimulates melanopsin-containing retinal ganglion cells resulting in signaling from the retina to the hypothalamus via the retinohypothalamic tract (separate from the optic nerve) terminating with the release of the neurotransmitter glutamate in the SCN (Zee and Manthena, 2007). These nerve impulses then signal the neurons of the SCN, through changes in gene expression, to relay information to sleep and wake promoting nuclei such as the VLPO and other monoaminergic nuclei (Zee and Manthena, 2007). Other *zeitgebers* include exercise, social interactions, eating and drinking.

Over a century ago, researchers showed that the injection of cerebrospinal fluid from a sleep-deprived dog into sleep satiated dogs promoted sleep (Legendre and Pieron, 1910). This eventually led to the other half of this two-process model – the homeostatic process (Borbely, 1982). The homeostatic process increases and decreases with wakefulness and sleep, respectively. Although numerous hypnotoxins, also known as somnogens, have been reported, including cytotoxins and prostaglandins, a large body of evidence suggests that adenosine epitomizes this homeostatic process (Bjorness and Greene, 2009). During wakefulness, adenosine progressively accumulates in the brain, specifically the basal forebrain (Bjorness and Greene, 2009). Heightened brain activity during wakefulness results in an increase in ADP resulting in a depletion of ATP and subsequently a surplus of adenosine (Bjorness and Greene, 2009). As the brain rests (i.e. sleep), adenosine levels decline as energy balance is restored through phosphorylation of ADP with adenosine (Bjorness and Greene, 2009). Interestingly, caffeine, one of the most widely available and consumed pharmacologic agents, antagonizes two of the four adenosine receptor subtypes, specifically the A_1R and the $A_{2a}R$, to promote wakefulness (Huang *et al.,* 2005).

This two-process model of a circadian and homeostatic process produces consolidated periods of wakefulness and sleep. Under normal conditions, the circadian process counters the building homeostatic pressures throughout wakefulness allowing for a consolidated period of wakefulness. And, the decline in both the homeostatic and circadian process during sleep provides for a consolidated sleep period. However, if an individual indulges in excessive caffeine intake, international travel, frequent and/or prolonged naps, this tightly balanced two process system

becomes dysfunctional, manifesting as the inability to sleep during the normal sleep period and/or inability to maintain wakefulness at desired times.

1.3 The advent of the polysomnography

The advent of the PSG, a study during which numerous biologic signals during a sleep period are collected facilitated the characterization of sleep stages and other physiologic processes as already discussed. The routine PSG acquires brain wave activity with EEG signals recorded by way of scalp electrodes; muscle activity with EMG signals with electrodes placed on the mentalis and bilateral anterior tibialis muscles; eye movement activity with EOG signals recorded from electrodes placed next to the eyes; cardiac rate and rhythm with electrocardiogram signals; blood oxygen saturations with pulse oximetry; and, respiratory activity with nasal and oral breathing devices and respiratory belt monitors. A routine PSG captures the entire sleep period, which includes the time it takes to fall asleep (i.e. sleep latency) and all awakenings occurring during the night (i.e. WASO). The PSG is an invaluable tool for the clinical evaluation of sleep complaints. It has allowed for the standardization of numerous disorders within sleep medicine such as obstructive sleep apnea and periodic limb movements of sleep. The PSG is still routinely performed as part of the clinical evaluation of sleep complaints as well as for research purposes.

1.3.1 Brain waves and sleep stages

Brain waves are recorded from scalp surface electrodes and are characterized by the amplitude and frequency of the waves. The slowest brain waves are delta waves, otherwise known as deep or slow wave sleep, having a frequency of approximately 1-3 Hz (cycles per second) and a peak-to-peak amplitude of >75 microvolts (Iber *et al.,* 2007). Theta activity with a frequency of approximately 4-7 Hz and low amplitude is the most common sleep frequency. Alpha activity, with a defined frequency of 8-13 Hz, is most prominent during relaxed wakefulness with the eyes closed. Opening the eyes or active mentation attenuates the amplitude of alpha activity. Other pertinent patterns of brain waves required to differentiate sleep stages include sleep spindles and K-complexes. A sleep spindle has a frequency of approximately 11-16 Hz with duration of at least 0.5 seconds and resembles a weaving spindle (i.e. a low amplitude wave which reaches maximum amplitude in the middle and ends with low amplitude). A K-complex is a biphasic wave that stands out from the background EEG activity with duration of at least 0.5 second.

The composite EEG, EOG, and EMG signals allow each 30-second epoch of sleep to be given a specific stage designation. The EEG is recorded from multiple locations over the scalp that are carefully measured based upon established guidelines (Iber *et al.,* 2007). Before the AASM introduced a scoring manual in 2007, the Rechtschaffen and Kales scoring system was the standard (Rechtschaffen and Kales, 1968). There continues to be discussion about which scoring rules should be used but for the purposes of this review, we will refer to the 2007 AASM scoring manual (Iber *et al.,* 2007).

Each epoch is designated with a specific sleep stage as follows: stage wake (W), NREM sleep stages N1, N2, and N3, and stage REM. An epoch is scored as stage W when more than 50% of the epoch has alpha rhythm (Figure 1.2). Stage N1 is scored when less than 50% of the epoch is comprised of alpha activity and replaced by theta activity (Figure 1.3). Stage N2 is scored when low amplitude, mixed frequency EEG activity in the theta frequency is intermixed with sleep spindles and K-complexes (Figure 1.4). Stage N3 is scored when at least 20% of the epoch is comprised of delta waves (Figure 1.5). Stage REM sleep is scored when theta-like activity is observed in combination with two other specific findings: periods of REM and continuous loss of muscle tone (Figure 1.6).
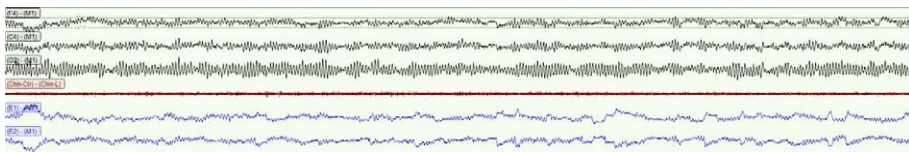
Figure 1.2. Stage wake (W). This is a 30 s epoch of stage W demonstrating alpha frequency brain waves (8-13 Hz). The top three channels are electroencephalogram (EEG) derivations with each channel representing a different location on the head. The fourth channel is an electromyogram (EMG) signal that represents muscle tone at the mentalis muscle. The last two channels are the left and the right electrooculogram (EOG) signals.
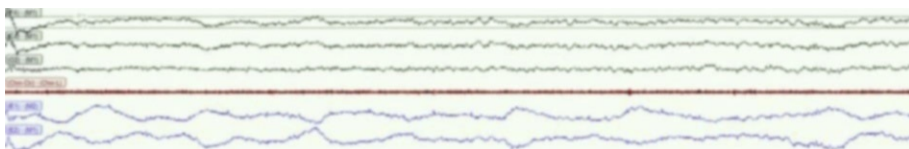
Figure 1.3. Stage N1. This is a 30 s epoch of stage N1 sleep demonstrating theta frequency brain waves (4-7 Hz). The chin electromyogram (EMG) channel remains elevated. The electrooculogram (EOG) channels show slow rolling eye movements. Slow rolling eye movements indicate a state of drowsiness and may be seen during Stage W through stage N2 sleep.
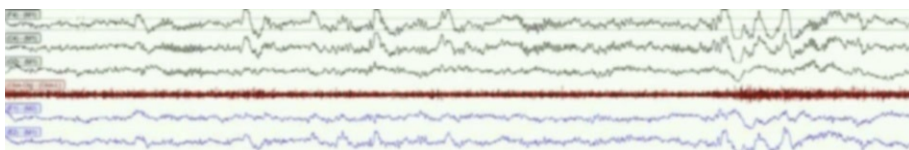
Figure 1.4. Stage N2. This is a 30 s epoch of stage N2 sleep demonstrating low amplitude, mixed frequency electroencephalogram (EEG) activity with sleep spindles and K-complexes. The chin electromyogram (EMG) channel remains elevated. Notice the disappearance of the slow rolling eye movements seen in stage N1 sleep.
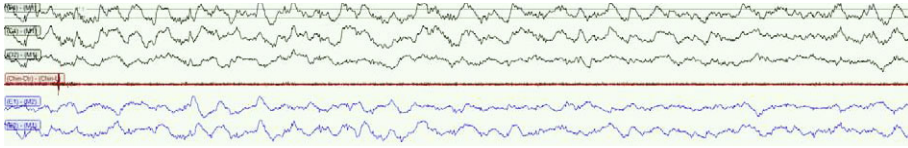
Figure 1.5. Stage N3. This is a 30 s epoch of stage N3 sleep demonstrating delta waves. The chin electromyogram (EMG) remains elevated but decreased in amplitude. The chin EMG may decrease in amplitude as one progresses from stage W to stage N3 but complete loss of muscle tone does not occur until REM sleep.
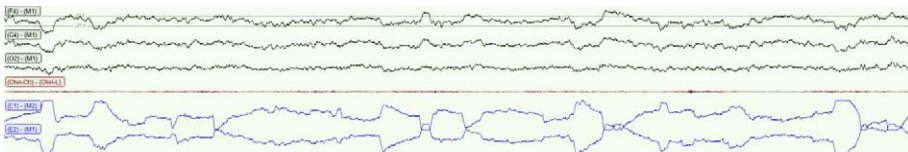
Figure 1.6. Stage R (REM sleep). This is a 30 s epoch of stage R demonstrating distinct findings in all three different channel types: electroencephalogram (EEG), electrooculogram (EOG), and electromyogram (EMG). The EEG signals demonstrate low amplitude, mixed frequency brain waves. The chin EMG shows very low muscle tone. The EOG channels (eye channels) show rapid eye movements.

1.3.2 Sleep architecture

Sleep stages are not equally distributed across the sleep period (Figure 1.7). There is an increased amount of stage N3 sleep during the first half of the sleep period that decreases as the night progresses while REM sleep builds throughout the night with the longest REM sleep episodes occurring in the latter half of the night. NREM and REM sleep demonstrate an ultradian cycle throughout the sleep period with each cycle lasting 90 to 120 minutes. Adults normally transition from wakefulness to stage 1 sleep and then progress into stages N2 and N3, and, ultimately REM sleep. This cycle normally occurs four to six times per night. The first few cycles are composed mostly of slow wave sleep while the latter cycles contain longer episodes of REM sleep. In young adults, NREM accounts for approximately 75% of the sleep period while REM sleep accounts for the remaining 25% of the sleep period. N1, N2, and N3 are not equally distributed within NREM sleep but rather account for 5%, 50%, and 20% of the sleep period, respectively.

1.3.3 Sleep and aging

Sleep architecture changes throughout the stages of life. REM or 'active' sleep has been recognized in utero but sleep spindles, delta waves, and K complexes are usually not present until approximately 2, 4, and 6 months, respectively (Anders *et al.,* 1971). Classification of newborn sleep relies heavily upon behavioral activity and other non-EEG correlates (e.g. muscle tone monitored at the chin electrodes) since the well-defined EEG criteria of NREM sleep are not present in newborns. There are essentially four states of infant sleep: quiet sleep, active sleep, indeterminate sleep, and
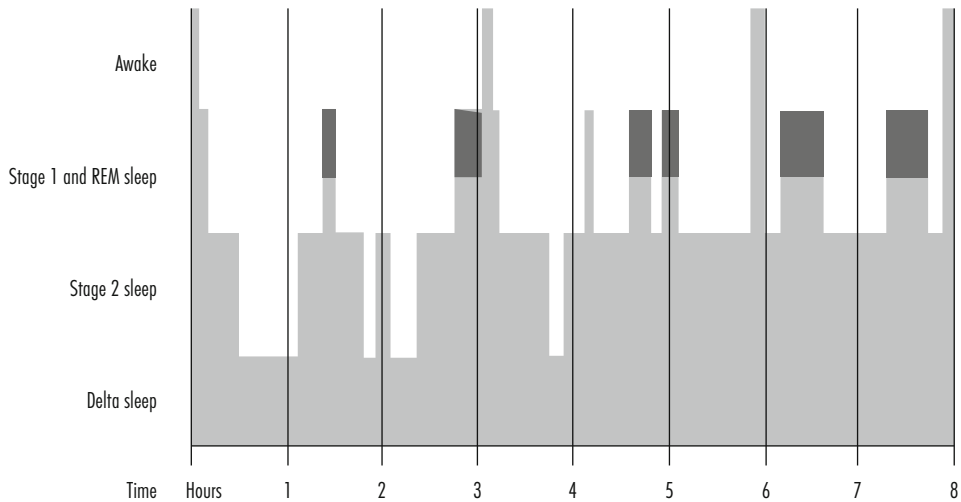
Stage 1 sleep and REM sleep (dark) are graphed on the same level because their EEG patterns are very similar

Figure 1.7. A normal sleep hypnogram depicting changes in sleep stages over the nocturnal sleep period for a young adult. Delta sleep (otherwise known as stage N3 sleep) occurs mainly in the first half hour of the night while rapid eye movement (REM) sleep progressively increases throughout the night in both frequency and duration. Note the non-rapid eye-movement (NREM) and REM sleep cycles approximately every 90 min (from Hauri, 1982).
EEG = electroencephalogram.

wakefulness (Anders *et al.,* 1971). Interestingly, newborns often transition from wakefulness immediately to REM sleep, otherwise known as active sleep; whereas, adults enter into stage 1 sleep and then progress into deeper stages of sleep prior to entering REM sleep. Also, NREM/REM cycles are much more frequent in infants but then gradually decrease to approximately 90-120 minutes. EEG characteristics of adult sleep are usually evident by 6 months of age but brain waves and parameters of sleep continue to develop throughout life. For example, sleep parameters that increase with advancing age are as follows:
1. sleep latency;
2. percentage of time spent in stage N1 and N2;
3. WASO.

On the other hand, sleep parameters that decrease with advancing age are as follows:
1. sleep efficiency, which is the percentage of time asleep divided by the total time spent in bed;
2. percentage of time spent in REM sleep and slow wave sleep;
3. REM latency;
4. Total sleep time, which is the total amount of sleep acquired in the sleep period.

Sleep needs vary from person to person and change across life. An infant might require 16 hrs of sleep per 24 hrs while a high school student might require 9 hrs of sleep per night. Childhood naps usually persist until around the age of 3 years. The average adult – although controversial – requires approximately 7.1 hrs per night. Interestingly, from a historical perspective, this number has decreased by at least one hour over the last century (Bliwise *et al.,* 1992; Webb and Agnew, 1975). Reasons for this decrease in sleep duration abound in today's society such as shift-work, international travel and work, computers, phones, texting, video games, and continuous television shows. With industrialization came environmental factors – especially artificial indoor light – that have allowed society to operate around the clock. And, now an overwhelming number of individuals operate in a sleep-deprived state. Subsequent chapters will address the effects of sleep deprivation on energy metabolism and insulin resistance.

1.3.4 Arousals and sleep instability

Sleep disorders, medical, and psychiatric diseases may lead to sleep fragmentation and altered sleep duration. The nearly universal finding among most sleep pathologies is that they lead to arousals and/or sleep state changes that ultimately disrupt sleep continuity. Arousals can be further broken down into cortical arousals, sub-cortical activation, and CAPS. Cortical arousals are described as abrupt changes in the EEG frequency (i.e. alpha, beta and/or frequency>16 Hz) that last for at least 3 s (Iber *et al.,* 2007). Sub-cortical activations such as changes in blood pressure and/or heart rate are often associated with these AASM defined cortical arousals. However, sub-cortical activations may occur independent of AASM defined cortical arousals (Orem and Barnes, 1980). Frequent arousals may lead to elevated cortisol levels. Patients suffering from insomnia, for example, may have elevated cortisol levels. Another EEG measure of sleep instability in NREM sleep is CAPS, which can be thought of as a marker of pre-arousal activation (Terzano *et al.,* 2001). Arousals and sleep instability may prevent an individual from attaining and maintaining deeper, more restorative stages of sleep such as SWS and REM sleep. An individual with frequent arousals may report sleeping seven to eight hours per night but still suffer from chronic, partial sleep deprivation.

The most common pathologic condition leading to repetitive and frequent arousals is obstructive sleep apnea (Figure 1.8). An obstructive apnea is due to a complete collapse of the airway during sleep, which may lead to a cortical arousal and/or decrease in the oxygen saturation. An individual with obstructive sleep apnea may have hundreds of arousals during sleep. Arousals and disruption of sleep may also result from esophageal reflux events, RLS, leg jerks during sleep (i.e. periodic limb movements in sleep), chronic pain, and many other conditions. Treatment of the underlying condition (e.g. healthier eating habits for gastroesophageal refluex, iron supplementation for RLS, weight loss and continuous positive airway pressure for sleep apnea, and medications for chronic pain) often leads to a decrease in cortical arousals, less disrupted sleep, and may even lead to a compensatory increase in SWS and REM sleep – in other words, the body's way of 'catching-up' on sleep.
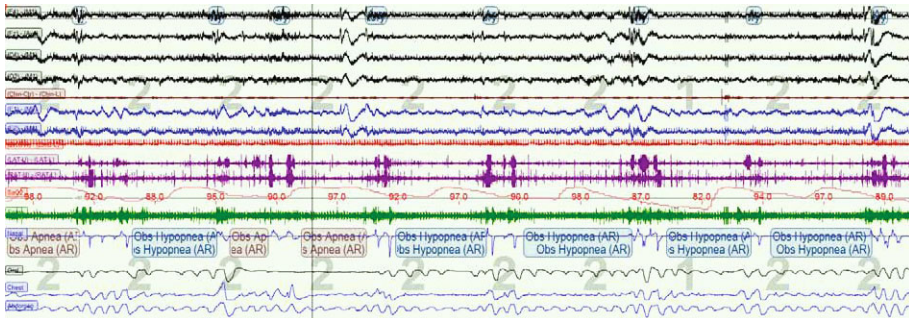
Figure 1.8. This is a 300 s (5 min) example of a subject with severe sleep apnea with cyclical respiratory events followed by oxygen desaturations and arousals.

In the following chapters, experts in the field of sleep medicine and nutrition will address most, if not all, of these categories with an emphasis placed upon the manifestations of disorders such as sleep deprivation, altered metabolism, insomnia, and napping. Research has significantly advanced our understanding of the neurologic control of sleep. However, many questions remain in sleep medicine: why do we sleep; why is sleep divided up into NREM and REM sleep; what are the long-term effects of sleeping less and less; and, the list goes on of unanswered questions. Many questions remain but what is known is that proper diet, nutrition, and sleep are imperative to leading a healthy life.

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Summary points

- The diagnosis of insomnia requires a report of poor sleep and a related loss of function on the day that follows.
- Insomnia is typically associated with another medical or psychological problem such as chronic pain or depression but can also be a primary or lifelong disorder.
- Primary insomnia seems to be related to an inability to relax and is often associated with physiological arousal such as increased heart rate and continuing mental activity.
- Primary insomnia has been shown to increase the likelihood of development of other medical and psychological problems such as depression and hypertension.
- Drinks and foods including chocolate have been associated with insomnia in caffeine-sensitive individuals.
- Caloric restriction or nutritional deficits can be associated with insomnia.

Handbook of nutrition, diet and sleep

2. Insomnia

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Abstract

Insomnia is the most common sleep disorder. A diagnosis of insomnia requires both a report of poor sleep at night and residual daytime impairment associated with the poor sleep. Insomnia is associated with many other medical problems ranging from depression to any issue that causes physical discomfort or pain. Insomnia may be associated with a specific set of environmental conditions or a chronic and unremitting problem that is either primary or associated with another medical problem. Treatment of an associated medical problem like pain improves sleep in some but not all cases. Conversely, treatment for insomnia may improve other medical outcomes. Primary insomnia seems to be related to inability to down regulate arousal and is frequently characterized by increased metabolic rate, heart rate, or other physiological markers. Some research has shown that insomnia may therefore be related to the development of hypertension and other disorders related to physiological arousal. Relatively little work has linked nutrition with insomnia. Beyond associations between caffeine or stimulant use and poor sleep, there is limited work linking poor nutrition with poor sleep and improved nutrition with better sleep.

Keywords: sleep, sleep disorders, hyperarousal, sleep maintenance insomnia, sleep onset insomnia

Abbreviations

EEG	Electroencephalogram
ICSD-2	International classification of sleep disorders second edition
MMPI	Minnesota multiphasic personality inventory
MSLT	Multiple sleep latency test

2.1 Introduction

Insomnia is defined as a complaint of difficulty initiating sleep ('sleep onset insomnia'), difficulty maintaining sleep ('sleep maintenance insomnia'), or waking up too early without being able to return to sleep ('early morning awakening'). Patients may also complain of non-restorative or poor quality sleep. This problem occurs despite an adequate opportunity to sleep and is associated with a daytime impairment (American Academy of Sleep Medicine, 2005). Poor sleep can vary from night to night but is usually defined as insomnia if it takes 30 minutes or more to fall asleep or if total sleep time is less than 6 hrs and the poor sleep usually occurs on 3 or more nights per week. However, a formal diagnosis of insomnia also requires the presence of a daytime impairment. The ICSD-2 from the American Academy of Sleep Medicine (2005) lists nine types of daytime impairment associated with an insomnia complaint. These symptoms are as follows:

1. fatigue/malaise;
2. attention, concentration, or memory impairment;
3. social/vocational dysfunction or poor school performance;
4. mood disturbance/irritability;
5. daytime sleepiness;
6. motivation/energy/initiative reduction;
7. proneness for errors/accidents at work or while driving;
8. tension headaches, and/or GI symptoms in response to poor sleep;
9. concerns or worries about sleep.

Although patients with insomnia frequently feel that they are sleep deprived, insomnia differs from sleep deprivation because in sleep deprivation the reduction in sleep is related to a decreased opportunity for sleep and sleep returns to normal when a sufficient time becomes available. There are other individuals who have a reduced need for sleep so that they may only sleep 5-6 hrs per night without daytime fatigue or other impairment. These individuals are called short sleepers and are not given a diagnosis of insomnia.

Insomnia is the most common sleep disorder and one of the most common medical complaints. About 30% of the population of the United States report at least some of the elements of insomnia such as difficulty falling asleep or staying asleep, and about 10% of the population complain of chronic insomnia with residual daytime deficits as earlier described (Johnson, 2006; Mellinger *et al.*, 1985; Ohayon, 2002). About 69% of patients being seen in a primary care practice reported at least occasional insomnia (Schochat *et al.*, 1999). However, the incidence of insomnia also

increases with age. Overall in the elderly, 57% complained of chronic insomnia, and only about 12% of respondents reported normal sleep (Foley *et al.*, 1995). Also, adult women report insomnia about 50% more often than men (Mellinger *et al.*, 1985), and there is a higher prevalence of insomnia in persons of lower socioeconomic status, the unemployed, and divorced, widowed, or separated individuals (Ohayon, 2002).

2.2 Differential diagnosis of insomnia

Insomnia is commonly associated with numerous psychiatric or medical problems but can also be related to behavioral and situational issues. The Diagnostic Manual of Mental Disorders simply classifies insomnia as primary or as related to another medical condition (or more recently 'comorbid' insomnia; American Psychiatric Association, 1994). The ICSD-2 from the American Academy of Sleep Medicine (2005), contains eleven separate sub-classifications for insomnia. At a simpler level, causes of insomnia can be divided into four major categories which will be dealt with below.

2.2.1 Situational insomnia

Environmental stimuli, including almost any change to habitual sleeping times, surroundings, or sleep preparatory routine can have a negative impact on sleep. Acute stress, pain, or other discomfort can reduce sleep quality. Situational insomnia is triggered by a specific onset event and has a time course of less than three months (American Academy of Sleep Medicine, 2005). Situational insomnia usually resolves when the situation returns to normal. Situational insomnia is reported more frequently in females than males and more frequently in older adults (American Academy of Sleep Medicine, 2005). Events that can produce situational insomnia are:

1. changes in bed room (bed, furnishings, light, temperature, occupants);
2. changes in type or level of background noise;
3. stressful life events such as arguments, loss of a loved one, divorce, loss of employment, or work or school demands;
4. illnesses (particularly any illness or injury resulting in pain or discomfort);
5. use of or withdrawal from caffeine, nicotine, alcohol or foods or substances containing these substances ;
6. ingestion of medications that contain stimulants (theophylline, beta blockers, corticosteroids, thyroxine, bronchodilators, or withdrawal from central nervous system depressant medications);
7. changes in time, time zone, work schedule, or work shift.

2.2.2 Behavioral or learned insomnia

Many individuals develop poor sleep in response to a stressful experience. Spielman (1987) has proposed that, if a patient responds to a situational insomnia event in an inappropriate manner by spending more time in bed, using alcohol, starting to have irregular sleep habits, or engaging in

other sleep inappropriate behavior, the poor sleep continues after the acute stress has passed and is then maintained by then inappropriate behaviors that have been learned. These patients may start to worry about their inability to fall or stay asleep or the consequences of poor sleep, and this further exacerbates the problem. The major factors associated with conditioned insomnia are: anxiety about sleep, intrusive thoughts or rumination while trying fall asleep, increased muscle tension or inability to relax while trying to fall asleep, ability to sleep better away from home, better ability to fall asleep at other times when not trying to fall asleep (American Academy of Sleep Medicine, 2005).

Other people develop poor sleep habits simply related to a chaotic lifestyle or inappropriate habits unrelated to stressful events. Poor sleep hygiene can range from poor diet choices such as consumption of caffeine or alcohol in close proximity to bed time to irregular sleep or waking times associated with shift work or college class schedules to increased activity in the evening. Clues to poor sleep hygiene include (American Academy of Sleep Medicine, 2005): improper sleep scheduling (frequent daytime napping, highly variable bed times or wake times, or spending excessive time in bed); routine use of caffeine, alcohol or nicotine in the period preceding bedtime; mentally stimulating, physically activating or emotionally loaded activities preceding bedtime; use of the bed or bedroom for nonsleep activities (eating, studying, watching television, planning, or reading); or uncomfortable sleep environment (light, noise, heat or cold, or disruptive pets).

Although diagnostically categorized separately, insomnia is the major complaint found in circadian rhythm sleep disorders. Circadian rhythm disorders, which involve violation of underlying sleep/wake rhythms by trying to shift the sleep period in time, can produce either difficulty falling asleep or poor sleep maintenance. Insomnia secondary to circadian rhythm disorders can be acute (as in 'jet lag') but may also be periodic, as in rotating shift work, or chronic, as seen in patients trying to go to bed earlier or later than their internal rhythm dictates to align with work or social requirements. Circadian rhythm disorders are listed here with behavioral problems because the sleep-wake rhythm is maintained and shifted with behavioral interventions such as bright light exposure and changes in activity patterns.

2.2.3 Insomnia associated with other medical problems

Perhaps 44% of chronic insomnia cases are associated with mental disorders (Ohayon, 2002), and insomnia precedes and predicts the development of psychiatric illnesses including major depression, anxiety disorders, and substance abuse disorders (Breslau *et al.*, 1996; Ford and Kamerow, 1989). One study reported that insomnia patients were 34 times more likely to develop a new psychiatric disorder such as major depression within one year when compared with individuals without insomnia (Ford and Kamerow, 1989). Insomnia is also reported as a major symptom in patients with psychiatric diagnoses. About 80% of depressed patients (Krystal, 2006) and patients with an anxiety disorder report insomnia as a symptom. Patients more frequently report the onset of insomnia prior to the development of a depressive episode than during or following the depressive episode, but insomnia more typically occurs concurrently (about 38% of the time) with the appearance of an anxiety disorder (Ohayon and Roth, 2003) or following the

appearance of anxiety (about 44% of the time). Insomnia is also common in patients at risk for substance abuse, in active abusers, and during withdrawal states. For example, one survey found that 13% of a representative community-based sample of 2181 Detroit residents had used alcohol in the last year to help them fall asleep (Johnson *et al.*, 1998). The prevalence of alcohol abuse/dependence was about twice as high in patients with a history of insomnia (Ford and Kamerow, 1989), and patients with insomnia were more than twice as likely to develop alcohol abuse in the next year (Weissman *et al.*, 1997). During withdrawal from alcohol, 60-91% of patients report insomnia as a continuing problem (Arnedt *et al.*, 2007). The relapse rate was twice as high (60%) in patients with a prior history of insomnia, and insomnia was the major predictor of relapse (Brower, 2003).

Insomnia is a frequent complaint from any patient suffering from any type of medical problem that produces physical discomfort or any psychological problem that is related to stress. This very broad statement supports the increased risk of insomnia in most medical disorders including patients with pulmonary disease, chronic pain, cardiac disease, hypertension, neurological disorders, gastrointestinal disorders or urinary problems (Taylor *et al.*, 2007) even when adjusted for depression, anxiety, and other sleep disorder symptoms, as assessed by screening questionnaire scores. Overall, 38% of patients with any medical problem also reported insomnia while only 8% of patients without other medical problems reported insomnia. Conversely and equally important, having insomnia increases the risk of having the above medical disorders and cancer. The same study reported that 86% of patients with insomnia reported another medical problem while only 48% of patients without insomnia reported another medical problem.

Insomnia is also a frequent presenting complaint from many patients who also have another sleep disorder. For example, 50-55% of patients undergoing evaluation for obstructive sleep apnea report insomnia symptoms (Banno and Kryger, 2006; Krell and Kapur, 2005) such as poor sleep, frequent awakenings, nocturia, or daytime deficits, One study found that 29% of older patients referred for an insomnia problem without symptoms of sleep apnea were found to have sleep apnea (Gooneratne *et al.*, 2006). This implies that the sleep history of insomnia patients, especially older individuals, needs to include evaluation for snoring and other signs of sleep apnea, and patients who are treated for sleep apnea may need further evaluation to determine if they have a separate insomnia problem that might require additional treatment. Other common sleep disorders associated with insomnia are restless legs, which cause discomfort requiring movement specifically at bed time (85% of patients with restless leg syndrome have difficulty falling asleep (Allen *et al.*, 2003)) and periodic limb movements, which are characterized by frequent limb movements often causing brief arousals or awakenings that can produce sleep maintenance insomnia or daytime sleepiness.

Finally, insomnia can be related to many treatments used for medical problems. Medications that may cause insomnia include stimulants, anorectics, beta antagonists, calcium channel blockers, corticosteroids, and antidepressants (Schweitzer, 2010). It is well-known that stimulants such as caffeine used in the evening produce insomnia. However, respiratory stimulants, such as theophylline taken in the evening, can also cause insomnia. Appetite-suppressing medications

can produce insomnia by virtue of their central stimulant properties. Medications such as methylphenidate or amphetamines, commonly used to treat attention deficit disorder, are stimulants that are associated with insomnia. Beta antagonists such as propranolol, metoprolol, and pindolol may produce sleep onset insomnia or increased awakenings and dreams. Antidepressant medications such as protriptyline and fluoxetine, may produce insomnia (Schweitzer, 2010). Corticosteriods such as prednisone, which produced insomnia in 50-71% of patients, and cortisol caused increased wakefulness during the night (Schweitzer, 2010).

2.2.4 Primary insomnia

Insomnia that is not associated with any other identifiable medical, psychiatric, or sleep disorder is classified as primary insomnia. These patients account for about 15% of all insomnia patients seen in sleep disorders centers (American Academy of Sleep Medicine, 2005; Ohayon, 2002). Despite being a small percentage of all patients with insomnia, primary insomnia patients have been studied in a majority of research projects because they are thought to represent a pure insomnia problem not mediated by other medical or psychiatric issues.

It is tempting to assert that almost everyone has an occasional night of poor sleep. However, studies of normal sleepers have shown that sleep is quite robust for some. An important question is what causes sleep to break down and whether individual sensitivities can be identified. Insomnia has been historically thought to develop secondary to an acute stress (Spielman *et al.*, 2005), and several types of stress have been examined in the laboratory. For example, sleeping in an unusual place, such as a sleep laboratory, is a mild stress that has been shown to produce statistically poor sleep that is considered situational insomnia. However, when individual data from a large group of normal sleepers sleeping for a first night in a sleep laboratory were examined, it was found that 25% of participants slept very well (they were asleep for an average of 97% of the recording time) while another 25% had poor sleep (they were asleep for an average of 82% of the night) (Bonnet and Arand, 2003). On the next laboratory night, adaptation had occurred, and both groups were asleep 92% or more of the night. These subjects were then exposed to other stresses including being put to bed 3 and 6 hrs earlier than normal or being given 400 mg of caffeine 30 minutes prior to bed on different nights, and the same situational insomnia pattern that was seen on the first laboratory night was repeated: putting the subjects to bed 3 hrs earlier than normal reduced sleep efficiency to 82% in the original poor sleepers but left it at 92% in then better initial group. Administration of caffeine reduced sleep efficiency to 61% in the original poor sleepers but left it at 82% in the better initial group. However, the important question was how these two groups of 'normals' whose sleep responded consistently in a similar manner to different types of stress were different in other dimensions. It was found that the subjects who reacted to the stress of spending a night in the sleep laboratory by having poor sleep did not differ in mood, personality, or other demographic measures from those subjects who showed little change in their sleep under the same stress. However, those subjects who had poor sleep in response to their first night in a sleep lab were found to have higher heart rates and decreased parasympathetic activity at baseline and greater sympathetic nervous system activation than the good sleepers after phase-advanced sleep. The implication is that some of us carry a predisposition

for increased sensitivity to stressors based upon greater underlying autonomic activation. It also seems logical that individuals with lower trait autonomic activation might tolerate stress more easily in a simple additive model, as it would take greater amounts of stress to move them into a pathological response (Salin-Pascual *et al.*, 2006). In the real world, sympathetic activation also tends to increase with age, physical deconditioning, and numerous medical problems and this could increase the predisposition to insomnia as individuals mature in our society. Of more importance, these latter conditions are chronic and could therefore be responsible for the development of chronic insomnia in predisposed individuals. The implication is that insomnia can be seen as a confluence of underlying physiological predisposition interacting with a range of stressors (that may include both cognitive/emotional stress and physiological activation) to produce insomnia on a given night in a given individual.

A predisposition to insomnia is also supported by several studies that have shown a strong genetic influence in insomnia (Beaulieu-Bonneau *et al.*, 2007; Heath *et al.*, 1990; Watson *et al.*, 2006). About 73% of primary insomnia patients have a history of insomnia in the family (Dauvilliers *et al.*, 2005; Heath *et al.*, 1990). One twin study showed a heritability estimate of 57% for insomnia (as contrasted with 73% for obesity and 38% for sleepiness) (Watson *et al.*, 2006), and evidence of association with specific genotypes is beginning to appear (Delisle *et al.*, 2010).

Studies comparing patients diagnosed with primary insomnia with controls have shown a number of differences. Primary insomnia patients cannot have a diagnosis of anxiety or depression by definition. However, study population comparisons have consistently shown that primary insomnia patients do present with significantly elevated scores in the direction of psychopathology in comparison with controls, as measured by the MMPI particularly in the dimensions of depression, anxiety, and concern with medical issues. Numerous studies have also documented that patients with primary insomnia have increased physiological activation compared with normal controls across numerous dimensions including increased whole-body and brain metabolic rate; increased heart rate, sympathetic nervous system activation, and decreased parasympathetic nervous system activation, as assessed by heart rate variability; increased high-frequency EEG (beta) activity; and abnormal hormone secretion (increased cortisol and norepinephrine and decreased melatonin) (Bonnet and Arand, 2010).

Because insomnia patients typically display both mood alteration and evidence of physiological arousal, identification of underlying causal factors has been more difficult. However, one study (Bonnet and Arand, 1992) examined the effects of increasing physiological arousal in the production of insomnia through the administration of caffeine 400 mg three times per day for a week in normal sleepers. Caffeine use increased physiological arousal, as measured by whole-body metabolic rate, and sleep efficiency declined significantly. During the initial days of caffeine use, subjects had elevated latencies to sleep onset on a daytime nap test (MSLT) and reported increased subjective vigor. However, by the end of a week of caffeine use, subjects reported significantly increased daytime fatigue despite an MSLT that remained significantly elevated as compared to baseline. Also, anxiety, as measured by the anxiety scale of the MMPI, moved significantly toward psychopathology by the end of the week. The finding that chronically elevated physiological

arousal would paradoxically lead to increased fatigue even while patients were less sleepy on the MSLT was an indication that physiological activation by itself could be responsible for the same paradoxical reports in patients with insomnia. The increase on the anxiety scale of the MMPI, a non-transparent trait measure of personality, offered evidence that cognitive and personality components frequently seen in patients with insomnia could be significantly influenced by a chronically increased level of central arousal. In another study, normal sleepers were given the same sleep pattern as a matched insomnia patients (a technician awakened or aroused normal sleepers whenever the insomnia patient aroused or awoke) for a week to determine if the poor sleep pattern by itself would produce the daytime symptoms that insomnia patients report (Bonnet and Arand, 1996). The results of the study indicated that normal sleepers given this 'insomnia' suffered from mild sleep deprivation but did not develop the changes in mood, personality, or physiological activation typically seen in insomnia patients. In a similar study (Bonnet and Arand, 1998b), it was hypothesized that if nocturnal sleep parameters produced the daytime dysphoria reported by patients with insomnia, then sleep maintenance insomnia patients who were kept awake even longer than usual during the night should have increased dysphoria during the following day. To test this hypothesis, patients with sleep maintenance insomnia were allowed only 80% of their already reduced total sleep each night for seven consecutive nights. This sleep reduction was accomplished by waking patients at the end of each quarter of the night if they accumulated more than 80% of their baseline sleep for that quarter of the night (while holding time in bed for the entire night at the baseline level). This paradigm produced very poor sleep (total sleep of 4.2 hrs on each night for the week). The further reduction of total sleep time resulted in a significant decrease in daytime MSLT values from 15.6 to 11.1 minutes. However, the 11.1-minute value is still considered 'normal' for the MSLT and compares well to the 11.1-minute sleep latency reported by Dinges *et al.* (1997) in normal young adults after baseline sleep. However, when these normal young adults then had their sleep limited to 5 hrs per night for 5 nights, their MSLT was reduced to 3.0 minutes. These results highlight that insomnia patients did become a little sleepier when their sleep was reduced but that the resulting sleepiness was still equal to normal sleepers at baseline and much less than that seen in normal sleepers after similar sleep loss. This result documents the degree to which hyperarousal in insomnia can mask sleep tendency. Of equal interest, insomnia patients did not report significant decreases in their sleep quality or show changes in their personality or physiological parameters consistent with more severe insomnia when their wake time during the night was increased by 2 hrs. One conclusion from such data is that reports of poor sleep quality and daytime dysphoria in insomnia patients were not directly related to their EEG sleep at all but rather to their abnormal arousal (Bonnet and Arand, 2003).

One key to understanding many medical disorders is the development of an animal model. Animal models are problematic for psychological problems but are common for physiological problems. However, as the diagnosis of insomnia currently requires a subjective complaint of insomnia, the development of an animal model needs to be carefully considered. In one recent experiment where rats were exposed to acute stress (Cano *et al.*, 2008), it was found that the animals displayed both long sleep latency and reduced sleep time when allowed to sleep. These rats were sacrificed 5.5 hrs after exposure to the stress, and brain activity was significantly elevated

both in sleep promoting areas of the brain but also in the cerebral cortex, limbic system and parts of the arousal (specifically locus coeruleus) and autonomic systems in comparison with controls. These dual findings suggested that the rats were displaying 'simultaneous activation of the sleep and arousal systems' (Cano *et al.*, 2008: p. 10173) These same animals also showed increased high-frequency EEG (gamma) during their sleep recordings after the stress. In another part of the experiment, lesions in the limbic system or arousal system were associated with improved sleep and normal gamma during sleep after the same stress. These findings suggest that insomnia is a condition where the brain is both asleep and activated at the same time and where the activation is mirrored by many physiological measures. These data imply that insomnia may be a problem of inappropriate activation and that treatment could be directed to decrease arousal.

The potential medical impact of insomnia has not been previously appreciated because of lack of understanding of the need for sleep and because many patients who report insomnia sleep fairly well based upon standard sleep recording techniques. However, if insomnia is associated with autonomic activation (Bonnet and Arand, 1998a), patients with chronic insomnia would be expected to have an increased risk of hypertension (Suka *et al.*, 2003) and cardiac disease including heart attack (Bonnet and Arand, 2007), and many studies have reported these associations. One recent laboratory sleep study has shown that patients with primary insomnia without sleep disordered breathing had significantly higher diastolic blood pressure than controls both at night and during the day with significantly higher systolic blood pressure at night (Lanfranchi *et al.*, 2009). A risk assessment study that also measured and controlled sleep disordered breathing (Vgontzas *et al.*, 2009) showed that patients with primary insomnia and short sleep times (compared with normal sleepers having short sleep times) were at increased risk for the development of hypertension. Such data suggest an underlying mechanism to explain why patients with insomnia have a higher incidence of several medical problems compared with controls and imply that successful treatments should both improve sleep quality and decrease risk for these disorders.

2.3 Insomnia and nutrition

With a few exceptions, research linking insomnia with nutrition is sparse. Because insomnia has been linked with sympathetic activation, foods containing caffeine including drinks and chocolate would be expected to be associated with poor sleep in individuals sensitive to caffeine, and these expectations have generally been confirmed (Bonnet and Arand, 1992, 2003), and are described in more detail in Chapter 22.

However, there are few studies and very limited support for strong relationships between many other nutritional sources and insomnia. If fact, feelings of support for nutritional variables have been weak enough that one major research study used improved nutrition as a non-active control condition. Reynolds *et al.* (2010) hypothesized that mild sleep restriction (a common treatment for patients with insomnia) in an elderly non-insomnia group would consolidate sleep and improve daytime function compared with an 'attention' control group that was seen as often

but only given nutrition counseling information during their lab visits. Over two and a half years of follow up visits, the nutrition group actually increased their time in bed and time asleep while maintaining similar levels of medical illness and health-related quality of life while the sleep restriction group had decreased time in bed (as expected) and increasing levels of medical illness and decreased health-related quality of life. There were no differences in a range of other activity, performance, and clinical measures. This led to two possible interpretations of the data. Either nutrition was helpful in maintaining sleep and health status or, alternatively, mild sleep restriction produced decrements in health status. While either could explain the results, the authors primarily discussed the outcome as a probable result of reduced sleep despite the fact that actual time spent asleep in the sleep restriction group at the end of the study was 5 minutes longer than at the pre-intervention baseline.

If improved nutrition is associated with longer sleep times, then it would imply that nutritional deficits should be associated with insomnia. At one level, nutritional deficits may be associated with stress that would provide a separate pathway to insomnia. However, Karklin *et al.* (1994) showed that a 1-month diet with significant caloric restriction produced weight loss in conjunction with a decrease in T3, a decrease (lower) in minimum body temperature during sleep and changes in sleep that included an increased sleep onset latency and decreased slow wave sleep. While the increase in sleep latency did not produce a complaint of insomnia, it is consistent with some reports of poor sleep during periods of caloric restriction. Studies of patients with eating disorders such as anorexia nervosa frequently but not always have increased wake time during sleep (Lauera and Krieg, 2004). More information can be found in Chapter 9.

In another study with a counter-intuitive outcome, Lichstein *et al.* (2008) examined supplemental vitamin use and sleep in a questionnaire study and found that respondents taking multi-vitamins reported more awakenings and increased wake time during sleep compared with respondents who took no vitamins. The awakening finding remained when using age as a covariate and controlling for sex and race. A specific association of vitamin use and insomnia complaint was of borderline statistical significance ($P<0.06$), but the study cannot rule out the possibility that people with poor sleep were more likely to start using vitamins to account for the described relationship.

Another study looked at lifestyle modifications such as improved nutrition, reduced stress, or increased physical activity on the incidence of insomnia in a complimentary medicine practice. After a 4-week program, sleep was most improved in those with increased physical activity and in those with a lower body mass index. Changes in alcohol use did not influence these results but there was some benefit from decreases in the use of coffee or tea (Merrill *et al.,* 2007).

L-tryptophan from natural food sources and as a supplement has been studied in insomnia patients for over 20 years. A recent review (Sarris and Byrne, 2011) suggests that L-tryptophan has mixed evidence for benefit in patients with insomnia but that there is little evidence for benefits from valerian or other herbal medicines. L-tryptophan studies are described in more detail in the section on Tryptophan and sleep.

Acknowledgements

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Summary points

- Diphenhydramine and doxylamine are histamine H_1 receptor antagonists commonly found in over-the-counter (OTC) sleep aids that purport relief of sleeplessness.
- There is limited objective data to support the effectiveness OTC sleep aids. Care should be used when taking H_1 antihistamine concurrently with sedative hypnotic medications and/or alcohol.
- Sedative benzodiazepine receptor agonists (BzRA) are very effective in treating insomnia. However, BzRA alters sleep architecture (e.g. decreases in slow wave sleep) and are associated with side effects (e.g. rebound insomnia, amnesia, and next day sedation) depending on their half-life.
- Nonbenzodiazepines receptor agonists (nonBzRA) have a lower risk of rebound insomnia and next day sedation.
- NonBzRA generally preserve sleep architecture and can be prescribed according to the specific insomnia symptoms being expressed.
- Insomnia management also includes off-label use of antidepressants. At doses lower than that used for depression, sedative antidepressants have limited objective data to support their efficacy and safety in treating insomnia in nondepressed patients.
- Antidepressants are effective in ameliorating insomnia, associated with concomitant depressive symptoms.
- Alcohol is a common self-administered treatment for sleep disturbances. The initial sedative effects of alcohol occur at the beginning of the sleep period.
- Alcohol metabolism causes sleep to become fragmented during the latter part of the sleep period. The abuse liability of alcohol makes it a poor choice as a sleep aid.
- Herbal supplements are often used as a self-treatment for a number of aliments. Herbal supplements studies have inconsistent clinical findings for their effectiveness as an insomnia treatment.
- Some herbal supplements have potential side effects if taken alone or concurrently with other herbal supplements, some prescriptions and/or OTC medications.
- Melatonin plays a role in the regulation of circadian rhythms. However, little data supports the efficacy of melatonin supplements in treating primary insomnia.
- The melatonin receptor agonist ramelteon is shown to be effective in treating sleep onset insomnia.
- An investigational trial studying the role of orexin (hypocretin) on the sleep wake cycle is a promising area of research. Orexin is a peptide that promotes wakefulness.
- Antagonism of the orexin system is being studied as a treatment for insomnia.

3. Insomnia and sleep medications

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Abstract

Insomnia is a highly prevalent sleep disorder. Efficacious pharmacological intervention can improve sleep by decreasing sleep onset, improving sleep maintenance, increasing sleep duration and sleep efficiency. Sedative hypnotics used to treat insomnia include benzodiazepine, nonbenzodiazepine and melatonin receptor agonist. The data supporting the effectiveness of over-the-counter sleep aids, herbal supplements and sedating antidepressants as insomnia treatments is limited and inconsistent. In no circumstances, alcohol is advised as a sleep aid. The appropriate choice of insomnia treatment must consider symptoms, harmful side effects, tolerance and dependence.

Keywords: sedatives, hypnotics, sleep initiation and maintenance disorders, primary insomnia

Abbreviations

5HT	Serotonin
BzRA	Benzodiazepines receptor agonist
CNS	Central nervous system
GABA	γ-aminobutyric acid
NonBzRA	Nonbenzodiazepine receptor agonist
OTC	over-the-counter
PSG	Polysomnography
REM	Rapid eye movement
SCN	Suprachiasmatic nucleus
SSRIs	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressants

3.1 Introduction

Insomnia is a prevalent disorder characterized by both nocturnal symptoms and daytime consequences. Sleep disturbances consist of difficulties with sleep initiation, sleep maintenance, waking earlier than intended raise time, and/or nonrestorative sleep despite adequate opportunity and circumstance for sleep. Increased risk for mood disturbances, poor work performance and reduced concentration are among insomnia consequences. For many with acute insomnia, recovery occurs after the precipitant situation resolves. For others, insomnia symptoms may exist for 30 days or more, or with periods of remission and relapse, predisposing one to chronic insomnia (National Institutes of Health, 2005).

Common insomnia self-medicated treatments include OTC sleep aids, herbal supplements, and alcohol. Prescription pharmacotherapy consists of several drug classes: sedating antidepressants, melatonin, benzodiazepine and nonbenzodiazepine receptor agonist. Chronic insomnia treatment with long-term pharmacotherapy insomnia may be insufficient and to some controversial. Potential therapeutic limitations include issues of tolerance, dependence, next day sedation and rebound insomnia with discontinuation. Historically, OTC and prescription medications were generally indicated for transient or short-term insomnia. With the availability of numerous insomnia treatments of varying efficacies and side effects, individualized treatment should consider the insomnia type and/or co-morbid conditions.

3.2 Antihistamines

An immune response to a normally innocuous substance (e.g. pollen, dust) can cause the release of histamines, which generates the classic allergic response. Antihistamines are indicated for effective control of running nose, sneezing and hay fever by inhibiting the contraction of respiratory smooth muscles, blocking histamine induced capillary permeability, and providing

relief of allergy symptoms. In terms of sleep wake function, these drugs block histamine receptors, a major alerting CNS neurotransmitter. First generation H_1 receptor antihistamines are lipophilic and cross the blood brain barrier to antagonize cholinergic muscarinic, alpha-adrenergic and serotoninergic receptors. Second generation antihistamines do not enter the brain well and have a greater selectivity for peripheral as opposed to central histamine receptors and hence do not cause sedation.

3.2.1 Diphenhydramine and doxylamine

A major effect of histamine H_1 receptor antagonism is sedation and this, in part, mediates the sedative activity of many OTC sleep aids (Table 3.1). The number of controlled trials that support diphenhydramine and doxylamine efficacy in terms of patient reports or PSG are limited. For insomnia, diphenhydramine is taken 30 min prior to bed and peak plasma concentration occurs within 2-3 hrs after administration. Diphenhydramine administration (50 mg) for one to two weeks, significantly reduced subjective reports of sleep latency, number of awakenings, increased sleep duration and sleep efficiency (sleep time/time in bed) with improvements in sleep quality (Glass *et al.,* 2008; Morin *et al.,* 2005; Rickels *et al.,* 1983). In psychiatric patients with insomnia, nightly diphenhydramine (12.5-50 mg) administration for two weeks produced similar self-reported hypnotic efficacy. Overall, improvements in sleep were significantly greater in those who never received prior insomnia treatment (Kudo and Kurihara, 1990). In contrast, in a 2 week placebo-controlled clinical trial of mild insomniacs, diphenhydramine (50 mg) showed a

Table 3.1. Histamine H_1 receptor antagonist in over-the-counter (OTC) and prescription drugs (Howell *et al.,* 2011; Krystal., 2009).

Generic name	Indicated uses	Hypnotic doses (mg)	$t_{1/2}$ (hrs)	Histamine H_1 receptor antagonist preparations
diphehydramine	motion sickness, cough relief, insomnia	25-50	5-11	Benadryl®, Dramamine®, Unisom SleepGel®, Nytol®, Tranquil® Nighttime Sleep Aid
doxylamine	allergies, antitussive, antiemetic, hypnotic	25	10-12	Unisom SleepTab®, Equate Sleep Aid®, Nighttime SleepAid®, Vicks Nyquil® Cold & Flu Relief, Alka-Seltzer Plus Night-Time Cold Medicine®
promethazine	allergies, control nausea and vomiting, cough and colds	12.5-25	10-19	Romergan (Phenergan), Phenergan with codeine, Promethegan

$t_{1/2}$ = elimination half life; OTC = over-the-counter; H = histamine receptor.

significant reduction in their subjective ratings of insomnia severity when compared to baseline. No significant differences between drug versus placebo in PSG defined measures of sleep latency, total sleep time, and sleep efficiency were found (Morin *et al.,* 2005). Objective and subjective measures of diphenhydramine efficacy have shown tolerance development following 3 days of administration (100 mg) in healthy male volunteers without sleep disturbances (Richardson *et al.,* 2002). At doses higher than that recommended for hypnotic effects, these results provide evidence of tolerance development and that diphenhydramine should be limited to short-term use (≤2 weeks).

Doxylamine is also used as a short-term insomnia treatment. As a sleep aid, doxylamine is taken 30 min before retiring to bed. Sleep is usually achieved within 45 to 60 min after oral administration with peak plasma concentration occurring after 90 min. Taken at bedtime, doxylamine causes high waking plasma levels and consequent residual daytime sedation due to its prolonged half-life (Stahl, 2008a). Patient reports showed that one-week doxylamine (25 mg) significantly decreased sleep latency, nocturnal awakenings, sleep duration and quality (Rickels *et al.,* 1984). At this writing, there are no identified published objective efficacy studies of doxylamine in treating primary insomnia.

Diphenhydramine and doxylamine are combined with various other medications to provide multiple symptom relief. Advertised as relief of sleeplessness associated with pain, in the United States, diphenhydramine preparations include analgesics, such as acetaminophen (Tylenol® PM), ibuprofen (Advil® PM), and aspirin (Bayer® PM). Doxylamine combined with various cold preparations provide relief of insomnia and cold symptoms (Vicks NyQuil Cough®, Safetussin® PM). The use of nighttime sleep aids containing histamine H_1 receptor antagonist does not warrant their use for allergy relief and cold or allergy medications should not be taken for sleep disturbances.

Patients with concomitant hypertension, cardiovascular and/or respiratory disease should use precaution when taking diphenhydramine or doxylamine. Additive CNS effects occur when H_1 antihistamines are taken concurrently with alcohol, other sedative/hypnotics, anxiolytics, narcotic analgesics and neuroleptic drugs. Similarly, significant interactions may occur if these drugs are taken concomitantly with anticholinergic agents or tricyclic antidepressants. Geriatric patients and those sensitive to sedative and anticholinergic properties of H_1 antihistamines should use caution when using diphenhydramine or doxylamine. Commonly reported side effects are next day drowsiness, grogginess, dry mouth, and tiredness (Meoli *et al.,* 2005).

3.3 Benzodiazepines receptor agonist and nonbenzodiazepine receptor agonist hypnotics

3.3.1 Benzodiazepine receptor agonists

BzRA are among the most widely used drugs in medicine mainly prescribed as hypnotics or anxiolytics. These drugs exert their effects by binding nonselectively at the junction between the alpha and gamma subunits within $GABA_A$ receptor complex and act as positive allosteric modulators of GABA. BzRA have a wide array of therapeutic uses including myorelaxant, anticonvulsant and as a presurgery anxiolytic. In general, BzRA improve sleep by shortening sleep onset latency, decreasing nocturnal awakenings and increasing total sleep time. However, BzRA produce changes in sleep architecture by decreasing time spent in deep sleep (stage 3 sleep or slow wave sleep), increasing stage 2 sleep and at higher doses mildly suppressing REM sleep.

In terms of hypnotics, BzRA are broadly classified in terms of their half-lives as short (1-4 hrs), intermediate (4-10 hrs), or long acting (>10 hrs). The rate of elimination is a major factor in determining the duration of effects. In the United States, the Food and Drug Administration (FDA) approved five BzRA for insomnia management: estazolam, flurazepam, quazepam, temazepam and triazolam (Table 3.2). Triazolam has a short duration of action, which makes it ideal for sleep onset insomnia with minimal residual next day sedation. The major side effects of short acting BzRA include anterograde amnesia (amnesia subsequent to drug administration) and rebound insomnia (the worsening of insomnia symptoms relative to the start of treatment). Rebound insomnia can be minimized with the gradual tapering of doses over a several nights as opposed to abrupt discontinuation or the use of lower doses. Hypnotics with short half-lives enable the clearance of active metabolites prior to morning rising reducing hangover effects, but may result in lack of efficacy with sleep maintenance (Stahl, 2008a,b). Intermediate acting hypnotic BzRA are best suited for sleep onset and sleep maintenance insomnia. Longer acting BzRA are best indicated for insomnia accompanied with anxiety. BzRA with long half-lives result in drug accumulation with chronic use. Residual next day effects include sedation, increase fall risk and fractures in elderly patients, impairments in cognitive and motor performance. If the half-life matches or slightly extends the duration of sleep time, the drug may continue to have hypnotic activity in the morning. Resulting in hangover effects, morning sedation and memory problems. Hypnotics with short half-lives enable the clearance of active drug or metabolites before the morning rising reducing hangover effects, but if the half-life is too short the drug may wear off prior to wake time, resulting in sleep maintenance difficulty (Stahl, 2008a,b).

In general, BzRA are recommended for short-term use (2-4 weeks) at the lowest effective dose to minimize adverse effects. Chronic BzRA use and/or use at higher than recommended doses may lead to tolerance, dependency and withdrawal symptoms upon discontinuation. BzRA CNS effects can be additive when combined with other sedative drugs (some antidepressants, H_1 antihistamines, neuroleptics, and alcohol). Patients with compromised respiratory function (e.g. sleep apnea, chronic obstructive pulmonary disease) are cautioned when taking BzRA as they may exacerbate respiratory disturbances. Those with a history of alcohol or drug abuse, or

Table 3.2. Benzodiazepines used to treat insomnia (Avidan and Zee, 2011; Howell *et al.*, 2011; Kryger *et al.*, 2010).

Generic drug (brand name)	Available doses (mg)	$t_{1/2}$[1] (hrs)	Duration of action	US FDA indication
triazolam (Halcion, Apo-Triazo)	0.125, 0.25	1.5-5.5	short	short-term insomnia management
brotizolam (Lendormin, Lendorm)	0.25	2.6-6.9	short	not available in the united states; short-term insomnia management
temazepam (Restoril)	7.5, 15, 22.5, 30	3.5-18	intermediate	short-term insomnia management
estazolam (ProSom, Nuctalon, Eurodin)	1, 2	8-24	intermediate	short-term for insomnia characterized by difficulty with sleep initiation, frequent nocturnal awakening and/or early morning awakenings
alprazolam (Xanax)	0.25, 0.5, 1, 2	12-20	intermediate	management of anxiety, nervousness, and tension associated with anxiety disorders and panic disorders and insomnia[2]
lorazepam (Ativan, Temesta)	0.5, 1, 2	12-16	intermediate	management of anxiety and insomnia[2]
clonazepam (Klonopin, Rivotril)	0.5, 1, 2	30-40	intermediate	treatment of seizures and relieves anxiety and panic disorder
nitrazepam (Alodorm, Remnos, Somnite)	5, 10	16-48	long	not available in the united states; short-term for insomnia characterized by difficulty with sleep initiation; sleep disturbances associated with physical or psychiatric disorders; anticonvulsant
flurazepam (Dalmane, Dalmadorm)	15, 30	2.3 active metabolites 47-100	long	short-term insomnia management
diazepam (Valium)	2, 5, 10	20-50 active metabolites 40 to 100	long	management of anxiety disorders; relief of skeletal muscle pain; may be used adjunctively in convulsive disorders, sleep disturbances[2]
quazepam (Doral)	7.5, 15	39 active metabolites 39 to 73	long	short-term for insomnia characterized by difficulty with sleep initiation, frequent nocturnal awakening and/or early morning awakenings

$t_{1/2}$ =elimination half life; FDA = Food and Drug Administration.
[1] $t_{1/2}$ values vary as a function of dose, and active metabolites; [2] off-label usage.

with muscular diseases are also cautioned when taken BzRA. Other BzRA are often prescribed off-label (nonapproved treatment) as hypnotics which is ill-advised given the lack of information regarding appropriate doses (Table 3.2). Outside of the United States, brotizolam, loprazolam, lormetazepam, flunitrazepam and nitrazepam are marketed as hypnotics.

3.3.2 Non-benzodiazepine receptor agonists

Concerns over BzRA adverse effects led to the development of nonBzRA. These drugs are structurally unrelated to BzRA, but bind specifically to the benzodiazepine subunits on the $GABA_A$ receptor complex. Non-benzodiazepine $GABA_A$ receptor modulators (zopiclone, zolpidem, zaleplon, and eszopiclone) differ in their pharmacokinetics and are commonly referred to as 'z-drugs' (Table 3.3). In comparison to long acting BzRA, z-drugs have shorter half-lives and are less likely to have next day residual effects. It is not clear if z-drugs have superior efficacy than shorter acting BzRA or if their efficacy is similar as there are few comparative studies evaluating multiple doses. Physician perceptions of improved efficacy and decreases in adverse effects compared to BzRA make nonBzRA a first line of intervention option (Stahl, 2008b). Further, nonBzRA are generally less disruptive to sleep architecture compared to BzRA.

Insomnia symptoms can vary from patient to patient and even within a patient over time. Some have difficulty with sleep onset, others with sleep maintenance or both. NonBzRA can be prescribed according to insomnia symptoms exhibited. Zaleplon has a half-life and peak plasma concentration of one hour and is rapidly absorbed after oral administration, therefore it is indicated for sleep onset. Similarly, zolpidem is also indicated for decreasing sleep onset. Hypnotics with short half-lives (1-3 hrs) such as triazolam, zaleplon, zolpidem can potentially wear off before intended wake time and are not indicated for sleep maintenance (Table 3.3). Evidence suggests that zaleplon can be taken (off-label) 4 hrs prior to scheduled wake time without residual next day hangover effects (Weitzel *et al.,* 2000).

In November 2011, the FDA approved treatment for insomnia characterized as awakening in the middle of the night with difficulty returning to sleep (Table 3.3). Zolpidem tartrate sublingual tablets (Intermezzo®) are a lower dose formulation of zolpidem. It is placed under the tongue to dissolve prior to swallowing. Drug administration should occur only when there is at least 4 hrs of bedtime before scheduled rise time. The recommended dose for women (1.75 mg) is lower than that of men (3.5 mg), because of women's lower metabolic rates. Both doses were shown to decrease sleep latencies on both polysomnography and subjective measures of efficacy.

For insomniacs with sleep onset and/or sleep maintenance difficulties, zopiclone, eszopiclone and zolpidem extended-release (ER) are indicated to treat these insomnia symptoms. Zolpidem ER formulation contains a bilayer in which the first layer dissolves quickly to promote sleep onset and the second layer dissolves slowly to help maintain sleep (Howell *et al.,* 2011). Neither zolpidem ER or eszopiclone are restricted to short-term use in their labeling. Long-term (12 months) efficacy studies with nightly zolpidem and eszopiclone use have shown minimal tolerance, dependence,

Table 3.3. Nonbenzodiazepine receptor agonist used to treat insomnia (Howell *et al.*, 2011; Stahl, 2008b, Kryger *et al.,* 2010).

Generic drug (brand name)	Drug class	Available doses (mg)	$t_{1/2}$ (hrs)	FDA indication
zaleplon (Sonata®)	pyrazolopyrimidine	5, 10	0.5-1	sleep onset
zolpidem tartrate (Ambien®, Stilnoct®, Stilnox®)	imidazopyridine	5, 10	1.4-4.5	sleep onset
zolpidem tartrate, sublingual tablets (Intermezzo®)	imidazopyridine	1.75, 3.5	1.4-3.6	awakening in the middle of the night, with difficulty returning to sleep.
zopiclone (Imovane®)	cyclopyrrolone	3.75, 7.5	5.26	sleep onset and nocturnal awakenings
eszopiclone (Lunesta®)	cyclopyrrolone	1, 2, 3	6	sleep onset and nocturnal awakenings
zolpidem tartrate ER (Ambien CR®)	imidazopyridine	6.25, 12.5	1.6-5.5	sleep onset and nocturnal awakenings

Nonbenzodiazepines in table are immediate release unless otherwise stated.

$t_{1/2}$ = elimination half-life; CR = controlled released; ER = extended released; FDA = Food and Drug Administration.

or withdrawal effects following discontinuation (Roehrs *et al.,* 2012; Roth *et al.,* 2005). In comparison, there are no long-term safety and efficacy studies of insomnia BzRA treatment.

The FDA have urged manufactures of sedative/hypnotics to include warnings of severe allergic reactions (anaphylaxis, angioedema) and complex sleep related behaviors (e.g. sleep eating, sleep walking, sleep sex and/or sleep driving) occurring following dosing. Reported complex sleep related behaviors can occur with no awareness or memory of the event the following day. These rare events may result from misuse or abuse of the sedative/hypnotic drugs and may occur even after taking a single dose or multiple doses. Greater incidents of bizarre sleep behaviors can occur if the sedative/hypnotic are taken concurrently with alcohol or other CNS depressant drugs. In general, the recommended initial dose of nonBzRA should be the lowest dose available in geriatric and debilitated patients, to minimize adverse effects related to impaired motor and/ or cognitive performance, and those with hepatic dysfunction. Common side effects include dizziness, headache, drowsiness, and bitter taste (zopiclone).

3.4 Antidepressants

Several antidepressants are used off-label for insomnia treatment (Table 3.4) Antidepressants can be characterized as sedating or energizing. Sedating antidepressants have potential sleep and analgesic properties. At doses much lower than that used to treat depression, sedating antidepressants are taken once daily at bedtime for insomnia. In general, antidepressants have limited objective data to support their efficacy or safety in treating insomnia in non-depressed patients, with the exception of low dose doxepin (Table 3.4).

Table 3.4. Antidepressants used to treat insomnia (Howell *et al.,* 2011; Kryger *et al.,* 2010; Mendelson, 2005; Stahl, 2008b).

Generic drug (brand name)	Antidepressant type	$t_{1/2}$ (hrs)	Hypnotic dose range[1] (mg)	Anti-depressant dose range (mg)	Receptors targeted
trazodone (Desyrel, Oleptro, Mesyrel)	phenylpiperazine/ atypical antidepressant	6-9	25-100	150-600	inhibits 5-HT reuptake, 5-HT_{2A}, H_1 and a_1 adren antagonist
amitriptyline (Elavil, Endep,Vanatrip, Tryptizol)	sedating TCA	10-28	10-100	100-300	5-HT_2 reuptake inhibitor and $5HT_{2A}$, $5HT_{2C}$, H_1 antagonist
nortriptyline Avantyl, Pamelor)	sedating TCA	16-90	2-10	75-100	5-HT_2 reuptake inhibitor and $5HT_{2A}$, $5HT_{2C}$ antagonist
imipramine (Tofranfl)	sedating TCA	9-20	10-25	50-150	H_1, a_1 adren, ACh, and 5HT reuptake blockage
mirtazapine (Remeron)	atypical antidepressant	20-40	7.5-30	15-45	a_2 adren, $5HT_{2A}$ $5HT_{2C}$ $5HT_3$, H_1 antagonist
trimipramine (Surmontil, Rhotrimine, Stangyl)	sedating TCA	24	25-100	50–150	H_1 5-HT_2, ACh, a_1 adren antagonist
doxepine (Adapin, Silenor, Sinequan)	sedating TCA	15-20 (active metabolites up to 80)	3-6	150-300	H_1 antagonist

[1] Therapeutic antidepressants doses are not standardized for use in nondepressed insomniac patients.

$t_{1/2}$ = elimination half life, 5-HT = serotonin; a adren = alpha adrenergic; ACh = cholinergic; NE = norepinephrine; H = histamine; TCA = tricyclic antidepressants.

3.4.1 Reuptake inhibitors

SSRIs, serotonin and norepinephrine reuptake inhibitors, and atypical antidepressants affect sleep quality and sleep architecture in different ways. Therapeutic doses of antidepressants used to treat depression, suppress REM sleep duration and increases REM latency in both depressed and healthy volunteers. SSRIs (e.g. fluoxetine, citalopram) are a poor choice for insomnia in that they increase stage 1 sleep, the number of nocturnal awakenings and awakening duration and decrease sleep time, observed in both insomniacs and healthy volunteers (Wilson and Argyropoulos, 2005). However, SSRI treatment may have some benefit if depression is co-morbid with insomnia. This however, is not usually the case as typically the insomnia predates the depression and is refractory to SSRI therapy. Norepinephrine reuptake inhibitors (e.g. venlafaxine, duloxetine) tend to be more stimulating than SSRIs and can potentially contribute to insomnia, partly due to increases in norepinephrine.

Nearly all antidepressants alter sleep in the opposite direction of the depression-related sleep disturbance, suggesting that sleep is an indirect biological marker of the drug's therapeutic activity. Sedating tricyclic antidepressants (e.g. clomipramine and imipramine) have REM suppressing effects with REM rebound upon withdrawal. Amitriptyline is effective in treating insomnia by decreasing sleep onset latency, nocturnal awakenings, increasing sleep duration and sleep efficiency. Amitriptyline tends to improve sleep in healthy normal volunteers, but not necessarily in depressed patients (Wilson and Argyropoulos, 2005). In primary insomniacs, trimipramine showed significant increases in PSG-defined sleep efficiency with minimal impact on sleep onset, nocturnal awakenings or REM sleep (Riemann *et al.,* 2002b). However, trimipramine is associated with feelings of being well rested in the morning.

3.4.2 Trazodone

Trazodone is the most commonly prescribed off-label treatment for sleep disturbances. As with most antidepressants, the effective dose for use in nondepressed insomniacs is not established. Most clinical trials that supports trazodone efficacy were conducted in depressed populations. At doses (25-150 mg) lower than effective antidepressant treatment (150-600 mg), trazodone has potent $5HT_{2A}$ antagonist properties, which contributes to its sedative properties. Structurally unrelated to other antidepressants, trazodone is characterized as an atypical antidepressant (Stahl, 2008b). There is limited evidence of trazodone hypnotic efficacy in treating insomnia in nondepressed patients and its mechanism of action is not fully understood. Clinical trials of PSG recorded sleep in nondepressed insomniac patients are scare and are limited in their clinical applications due to small sample size, problematic or no control groups. Trazodone efficacy in primary insomnia patients showed subjective improvements in insomnia symptoms, but PSG defined measures of sleep initiation, nocturnal awakenings and sleep duration were not significant (Mendelson, 2005). Commonly reported adverse effects occurred at doses of 75 to 500 mg which includes drowsiness, dry mouth, dizziness, nausea/vomiting, orthostatic hypotension and priapism. Thus, the adverse effects risk is unknown when trazodone is used as a low dose

hypnotic. Daytime sedation, risk of falls, psychomotor/cognitive dysfunction is of concern in geriatric patients taking trazodone (Mendelson, 2005).

3.4.3 Doxepin

Doxepin is the only antidepressant approved by the FDA for insomnia and specifically approved for sleep maintenance insomnia. Hypnotic doses of doxepin are substantially lower than that prescribed for depression (Table 3.4). At low doses, doxepin is a selective histamine H_1 receptor antagonist, which contributes to its hypnotic effects (Stahl, 2008b). PSG defined sleep measures show that doxepin decreases sleep onset, the frequency of nocturnal awakenings and their duration, resulting in increased sleep duration. Doxepin (3 and 6 mg) adverse effect profile is comparable to the placebo group (Roth *et al.*, 2007). This medication should be taken within 30 min of bedtime to avoid next day residual effects, and can be used in both depressed and nondepressed patients. Doxepin is one of two hypnotics not classified as a controlled substance (availability regulated due to its abuse potential) by the FDA.

All antidepressants have potential adverse effects. Sedating antidepressants can contribute to cardiac toxicity and daytime sedation due to their long half-lives. Exacerbation of restless legs syndrome and periodic limb movement disorder can occur with the use of TCA and SSRIs. SSRIs side effects include nausea, dry mouth, headache, diarrhea, restlessness, sexual dysfunction and the risk of serotonin syndrome. Serotonin syndrome is a potentially fatal disorder in which excessive CNS serotonin can produce symptoms of agitation/restlessness, diarrhea, rapid heartbeat, loss of coordination, nausea and vomiting.

3.5 Alcohol

Alcohol has a myriad of the effects on the CNS. It crosses the blood brain barrier to exerts its effects on the brain. As a depressant, alcohol enhances the inhibitory neurotransmitter GABA resulting in an overall decrease in brain excitability. The initial sedative effects occurring following alcohol consumption contributes to its self-medicated use as a sleep aid.

Alcohol use as a sleep aid is common. In a population-based survey, those with occasional insomnia used alcohol as a sleep aid an average of 3.6 nights per month, while chronic insomniacs used alcohol on average 6.8 nights per month. Within both populations, 67% described alcohol as being *very effective* or *effective* as a sleep aid (Ancoli-Israel and Roth, 1999). Alcohol causes dose-dependent decreases in sleep latency, increases in stage 3-4 sleep (slow-wave) within the first half relative to the second half of the sleep period and initial REM suppression. The completed metabolism of alcohol during the second portion of the night leads to rebound increases in sleep fragmentation or nighttime wakefulness, REM rebound, and increases in dreams and nightmares (Roehrs and Roth, 2001). The efficacy of alcohol in reducing sleep onset is not clinically important, when one considers the adverse effects of alcohol on sleep maintenance and architecture, especially during the latter portion of the night.

Tolerance to alcohol's sedative effects and dose escalation can lead to dependence and/or abuse. Furthermore, alcohol consumption can worsen and/or increase snoring, obstructive sleep apnea (Meoli *et al.,* 2005) and various parasomnias (disruptive sleep disorders that involve night terrors, sleep walking and nightmares) are exacerbated after alcohol consumption.

3.6 Melatonin and melatonin receptor agonist

Produced by the pineal gland, melatonin (N-acetyl-5-methoxytryptamine) synthesis and secretion occurs nocturnally in darkness and is inhibited by light, at specific times, which suggest its involvement in modulating circadian rhythms. Normal melatonin secretion starts in the evening and falls during the morning hours. Some people who have trouble sleeping may have low endogenous levels of melatonin or a delayed secretion, and that supplementing melatonin might assist with sleep. Riemann *et al.* (2002a) showed significant decreases in night-time melatonin concentrations in insomniacs and others have shown a delay in melatonin secretion. Double blind placebo controlled studies have failed to show the effectiveness of supplemental melatonin in treating primary insomnia. Melatonin was more effective in reducing sleep initiation in patients with delayed sleep phase syndrome than in primary insomnia (Buscemi *et al.,* 2004).

Exogenous melatonin (dietary supplement) is used for a variety of reasons: circadian rhythm sleep disorder, to combat jet lag, shift work disorder and for disrupted sleep, with inconsistent evidence of it effectiveness. Made synthetically, melatonin supplements are available in liquid, sublingual lozenge, immediate and time-release tablets. The half-life of melatonin ranges from 20 min to 2 hrs, however no dose is widely accepted for sleep disturbances. Reported doses that range from 0.3 to 5 mg are less likely to cause residual daytime drowsiness. Melatonin side effects include headache, odd taste, dizziness and poor sleep quality.

3.6.1 Ramelteon

Ramelteon is the first FDA approved selective melatonin receptor agonist that has high affinity for melatonin MT_1 and MT_2 receptors of the SCN. The SCN is responsible for controlling the behavioral and physiological circadian rhythm in mammals, including the sleep wake cycle. Activation of the MT_1 receptor is believed to regulate sleepiness and sleep initiation. Whereas MT_2 receptor activation mediates phase shifting effects of melatonin on circadian rhythms.

Ramelteon is indicated for sleep onset insomnia, due in part, to its short elimination half-life (see Table 3.5). In clinical trials, ramelteon has shown evidence of hypnotic efficacy with minimal next day residual effects, rebound insomnia and withdrawal effects upon discontinuation. Thus, the FDA does not classify this hypnotic as a controlled substance. PSG-defined measures of sleep efficiency show that ramelteon reduces sleep initiation and increase sleep duration in clinical trials of chronic insomniacs (Miyamoto, 2009; Stahl, 2008b). Ramelteon does not bind to the GABA receptor, thus its side effects differ from that of BzRA and non-BzRA. Incidences of side effects were mild to moderate in severity and well tolerated in clinical trials. Reported side effects

Table 3.5. Melatonin agonist used to treat insomnia (Arendt and Rajaratnam, 2008; Buscemi *et al.,* 2004; Howell *et al.,* 2011; Wade *et al.,* 2011).

Generic name (brand name)	Drug class	Hypnotic dose (mg)	$t_{1/2}$ (hrs)	Indication
Prolong release melatonin (Circadin®)	synthetic hormone supplement	2	3.5-4	short-term for insomnia characterized by poor sleep quality in patient ≥55 yrs
Ramelton (Rozerem®)	melatonin receptor agonist	8	1-2.6	sleep onset
Tasimelteon (VEC-162)	melatonin receptor agonist	50 mg had the greatest efficacy.	2.5	sleep disturbances related to circadian rhythm disorder

$t_{1/2}$ = elimination half life.

included somnolence, fatigue, dizziness, headache and next day residual effects however, these effects occurred at similar rates in both ramelteon and placebo treatment groups (Howell *et al.,* 2011).

3.6.2 Tasimelteon

Tasimelteon (VEC-162) is an experimental drug used for the treatment of sleep, circadian rhythm and mood disorders. Like Ramelteon, it has a high affinity for MT_1 and MT_2 receptors, which reduces sleep initiation, improves sleep maintenance and increases sleep efficiency relative to placebo. It also resets sleep patterns in a dose-dependent matter in those with sudden sleep schedule changes (Arendt and Rajaratnam, 2008; Rajaratnam *et al.,* 2009). Side effects were similar in both tasimelteon and placebo groups. Long-term safety and efficacy test are needed.

3.7 Herbal supplements

Herbal and dietary supplements are perceived as natural and therefore *inherently* safe. Dietary supplements have varied health benefit claims and are often taken for preventative and therapeutic purposes. In the United States, the FDA regulates herbal and dietary supplements under a different set of standards than conventional (OTC and prescription) medications. The supplement manufacture is responsible for the safety and quality control of their products, there are no standard guidelines on supplement dosage, administration, and variations occur among the same supplement from different manufactures. The FDA forbids the marketing and product labeling of supplements as treatment, prevention or cure for any disease or condition (US Food

and Drug Administration, 2009). The American Academy of Sleep Medicine, a professional medical society for clinicians, researchers and health care providers within sleep medicine, stance is that herbal supplements should not be used treat insomnia or any other sleep disorders unless approved by a physician.

Herbal supplements have reported side effects and minimal clinical findings to support their effectiveness. Many experimental studies of herbal supplements have significant methodological flaws that limit their reliability and application to clinical practice. Such flaws include absence of a placebo control group, small sample size, lack of objective measures, baseline differences in age and gender (Salter and Brownie, 2010).

Numerous herbal supplements have purported benefits as a sleep aid including valerian root, chamomile, kava kava, and St. John's wort (Table 3.6). Some herbal supplements, such as lemon balm or chamomile tea have minimal side effects when used in appropriate amounts. However, some supplements have serious adverse effects and can interfere with prescription medications or medical conditions.

3.7.1 Valerian

Valerian is a perennial plant, whose chemical ingredients vary depending upon the species (e.g. *Valeriana officinalis, V. edulis, V. sitchensis, V. angustifola and V. wallichii*) and the extraction method (using alcohol, water or both). The extraction method greatly influences active compounds in the final product. A possible mechanism in which valerian causes sedation is by inhibition of γ-aminobutyric acid GABA metabolism.

Literature reviews of valerian efficacy show that it may improve subjective sleep latency and quality, but these studies are not substantiated by rigorous scientific evidence (Bent *et al.,* 2006; Salter and Brownie, 2010). Overall, methodological problems (lack of objective data, small sample size, inclusion of normal sleepers vs. insomniacs, lack of a placebo control group, variations in valerian extract preparation and dose) limit the reliability and application of these findings to clinic practice (Salter and Brownie, 2010). Of the studies that used PSG defined measures of sleep, there were no consistent benefits of valerian effects on sleep (Bent *et al.,* 2006; Meoli *et al.,* 2005).

3.7.2 Kava kava

The methodological concerns of valerian are also seen in the literature related to kava kava. Kava *(Piper methysticum)* is a shrub with woody stems that is indigenous to the South Pacific islands. Kava has varied purported medical uses, including relief of anxiety, tension and sleep disturbances (Table 3.6). Limited evidence supports the efficacy of kava in treating primary insomnia. In sleep disturbances associated with anxiety, tension and restlessness of non-psychotic origin and stress-induced insomnia, kava showed subjective therapeutic effectiveness (Lehrl, 2004; Wheatley, 2001).

Table 3.6. Sedative herbal supplements used to treat sleep disturbances (DerMarderosian, 1999; Kuhn, 1999).

Herb	Plant parts used	Purported indication	Adverse effects
chamomile (*Matricaria chamomilla*; *Chamomilla recutita*)	flowering tops to make teas, liquid extracts, capsules, tablets or essential oils	sedative; reduces inflammation; gastrointestinal antispasmodics; anxiety.	contact dermatitis, anaphylaxis or allergic reaction in sensitive individuals; emetic (vomiting) if consumed in large qualities
hops (*Humulus lupulus*)	strobiles/seed cones	diuretic; sedative; treatment of intestinal cramping; analgesic; cystitis, menstrual problems and nervous conditions.	contact dermatitis in sensitive individuals
kava kava (*Piper methysticum*)	roots and rhizomes	insomnia; anxiety; restlessness; fights fatigue; urinary tract infection; menopausal symptoms	liver damage, skin drying and possible skin ulcers, hypertension, blood cell abnormalities with long-term use; exacerbates depression; should not be combined with sedative/hypnotics medications, including alcohol and sedative supplements; must be avoided in those with liver disorders
lavender (*Lavandula stoechas, L. dentata; L. angustifolia, L. latifolia*)	flowering tops	insomnia; antispasmodic; carminative; CNS depressant effects; alopecia areata (hair loss)	contact dermatitis in sensitive individuals; can increase or potentiate CNS depressant effects when used with sedative\hypnotics; topical use can cause breast development in young boys; poisonous if oil if taken internally
St. John wort (*Hypericum perforatum*)	flowering tops.	insomnia, restlessness, depressive moods; anxiety, hair loss, fatigue; menopausal-related mood symptoms; antiviral and antibacterial properties.	potentiate the effect of serotoninergic medications, not recommended with prescribed medications in general Causes photosensitivity; interacts with caffeine, antidepressants, sleep aids, OTC cough and cold remedies
valerian (*Valeriance officinalis*)	roots and rhizomes	insomnia; anxiety; lowers blood pressure; anti-inflammatory	intensify the effects of sedative/hypnotics; increases seizure activity when used with anticonvulsants

CNS = central nervous system.

Citing concerns over hepatoxicity (cirrhosis, liver failure) kava was removed from the market in some countries. In 2002, the FDA issued a consumer advisory of kava potential risk. Long-term kava use is associated with skin ulcers from extremely dry skin, hypertension and blood abnormalities. The use of sedative hypnotics (alcohol, antidepressants, etc.) can have CNS additive effects when used concurrently with kava.

3.7.3 St. John's wort

St. John's wort (*Hypericum perforatum*) is an aromatic perennial used in the self-medicated treatment of depression, anxiety and insomnia (Table 3.6). Hyperforin, the active ingredient in St. John's wort, inhibits reuptake of several neurotransmitters, namely serotonin, norepinephrine, and GABA, although the mechanism of this action is unknown (Meoli *et al.,* 2005).

Most clinical studies of St. John's wort focus on amelioration of depression symptoms. To date, no double-blind placebo controlled studies illustrate St. John's wort ability to ameliorate sleep disturbances. Side effects include gastrointestinal symptoms, dizziness, fatigue, allergic reactions and headache. St. John's wort increases anxiety, nervousness and exacerbates panic disorder symptoms when use is associated with caffeine and beta$_2$ agonist medications (used in the treatment of asthma and pulmonary diseases). St. John's wort limits the effectiveness of many prescribed medications such as anticoagulants, oral contraceptives, and some anticancer medications. When taken concomitant with some antidepressants it can contribute to serotonin syndrome.

3.8 Orexin (hypocretin)

Orexin, also referred to as hypocretin, is a neuropeptide neurotransmitter and orexin containing neurons are located within the lateral hypothalamus. The orexin system of the hypothalamus contributes to appetite and metabolism, thermoregulation and the sleep-wake cycle. The orexin system mediates wakefulness and antagonism is purported for its sleep promoting effects. MK-4305 (suvorexant) is an investigational drug with dual orexin (orexin$_1$ and orexin$_2$) receptor antagonism. In a 4-week double-blinded placebo controlled trial of primary insomniacs, MK-4305 produced a significant dose-response (10, 20, 40, and 80 mg) in PSG-defined measures of sleep onset and maintenance (Herring *et al.,* 2010). Orexin is generally well tolerated.

3.9 Conclusions

Insomnia treatment should involve the diagnosis and treatment of any co-morbid psychological and/or medical conditions that can cause or exacerbate insomnia symptoms as well as the insomnia per se. Monotherapy with pharmacological agents may be sufficient for short-term insomnia treatment but not ideal for chronic insomnia. Insomnia treatments entail medications that either enhance the inhibitory wake promoting neurotransmitter GABA$_A$ or block neurotransmitter

receptors that promote wakefulness, such as histaminergic, cholinergic, adrenergic and/or serotoninergic. The benefits of a pharmacological approach should outweigh adverse effect profiles. The lack of substantial data in antihistamine, antidepressants, and herbal supplements medications increase the need for comparative studies to define their role in insomnia treatment.

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Summary points

- Circadian rhythm sleep disorders (CRSDs) are caused by recurrent or persistent misalignment between the desired sleep schedule and the habitual circadian sleep-wake rhythm.
- *Zeitgebers* are environmental forces that reset the endogenous sleep-wake circadian rhythms.
- Entrainment is the alignment or synchronization of the endogenous biologic rhythms to exogenous time cues.
- Advanced sleep phase syndrome (ASPS) is characterized by a shift in the major nighttime sleep period to an earlier time in relation to desired or conventional bed times.
- Delayed sleep phase syndrome (DSPS) is characterized by a habitual delayed bedtime and equally delayed arising time.
- Irregular sleep wake rhythm (ISWR) has day-to-day variability in sleep and wake times due to absence of stable circadian sleep-wake rhythms.
- Free running disorder (FRD) is associated with an endogenous sleep wake rhythm with a periodicity of over 24 hrs, which results in progressive delays by about 1 hr or more each day.
- Actigraphy uses a wrist accelerometer that clinicians and researchers can use to identify periods of rest/sleep or activity.
- Treatments of CRSDs include phototherapy, chronotherapy, and melatonin.

4. Circadian rhythm sleep disorders

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Abstract

Circadian rhythm sleep disorders (CRSD) are caused by recurrent or persistent misalignment between the desired sleep schedule and the habitual circadian sleep-wake rhythm. This chapter will describe the clinical characteristics, consequences and treatment options of four common CRSDs, namely advanced sleep phase syndrome (ASPS), delayed sleep phase syndrome (DSPS), free running disorder (FRD) and irregular sleep wake rhythm (ISWR).

Keywords: advanced sleep phase syndrome, chronotherapy, delayed sleep phase syndrome, entrainment, free running disorder, irregular sleep wake rhythm, phototherapy, polysomnography

Abbreviations

ASPS	Advanced sleep phase syndrome
CRSD	Circadian rhythm sleep disorder
CTmin	Minimum core body temperature
DSPS	Delayed sleep phase syndrome
FRD	Free running disorder
ISWR	Irregular sleep wake rhythm
OSA	Obstructive sleep apnea
PSG	Polysomnography

4.1 Introduction

Biologic rhythms are essential to life and are ubiquitous, being present in most life forms. Since there is insufficient cellular energy to perform all physiologic processes at peak levels at all times, biologic functions tend to wax and wane during specific periods of a 24-hr day. For instance, peak expiratory flow rates tend to fall during the night, sudden cardiac death occurs most commonly between 6 am and 12 pm, and sundowning is seen in the early-mid evening. In addition, biologic rhythms preadapt the organism to daily recurring environmental events, such as the light-dark cycles of day and night, and may serve an evolutionary protective role.

Circadian (from 'circa' = about and 'die' = day) biologic rhythms display a periodicity of approximately 24 hrs. The human sleep-wake period cycles just slightly over 24-hrs, and, thus, if unaltered by exogenous forces, would occur progressively later each successive day. The process whereby environmental forces, referred to as *zeitgebers* (light and timing of meals and activities), reset the endogenous sleep-wake circadian rhythms to compensate for the slightly shorter 'clock' day and synchronizes it to the environmental day-night periods and to other endogenous biologic rhythms (e.g. body temperature rhythm) is called entrainment. Entrainment either phase advances or phase delays the target biologic rhythm depending on exposure to specific *zietgebers* and the timing of their exposure. Light given during the biologic day after CTmin will phase advance the circadian sleep-wake rhythm. Conversely, light given during the biologic night before CTmin will phase delay the sleep-wake schedule. Another clinically important *zeitgeber* is melatonin, which, if given in the early-mid evening will phase advance the sleep-wake cycle.

4.2 Circadian rhythm sleep disorders

CRSDs are caused by recurrent or persistent misalignment between the desired sleep schedule and the habitual circadian sleep-wake rhythm. Individuals with CRSDs can present with complaints of insomnia or excessive sleepiness, or both. Others may have non-specific gastrointestinal symptoms, fatigue, mental 'fogginess', or mood disorders. This chapter will discuss four common

CRSDs, namely advanced sleep phase syndrome, delayed sleep phase syndrome, free running disorder and irregular sleep wake rhythm.

## 4.2.1 Advanced sleep phase syndrome

In this syndrome, there is a shift in the major nighttime sleep period to an earlier time in relation to desired or conventional bed times, with sleep times habitually occurring early in the evening (e.g. from 6 pm to 9 pm) and wake times occurring in the early morning (e.g. from 2 am to 5 am). Affected individuals experience excessive sleepiness in the late afternoon or early evening and generally describe a marked inability to delay sleep time; they may, thus, present for evaluation of hypersomnia. Similarly, these persons also have spontaneous morning awakening that is earlier than desired and report being most alert in the morning. It is this inability to remain asleep until the desired morning waking time that may prompt them to seek treatment for terminal insomnia. Nevertheless, sleep itself is normal for age and undisturbed.

Several mechanisms can contribute to ASPS, including a deficiency in ability to phase delay coupled with an overly dominant phase advance capability. It has also been postulated that these individuals may possess a naturally faster circadian rhythm or have a profoundly short endogenous period length. Finally, a number of social and behavioral factors may contribute to its persistence, such as limited light exposure in the early evening (when the person may already be asleep) along with early morning light exposure following an equally early awakening, both of which will give rise to phase advancement of the sleep-wake rhythm.

Advanced sleep phase syndrome is estimated to affect 1% of middle-age adults, with lower prevalence among children and younger adults (Ando *et al.,* 1995). Onset of ASPS is typically during middle age or later, and both genders appear to be affected equally. Familial cases have been described, with certain individuals exhibiting the gene of familial ASPS, an autosomal dominant variant that is localized near the telomere of chromosome 2q (Toh *et al.,* 2001).

Circadian rhythm sleep disorders are evaluated using sleep logs or actigraphy, preferably performed over several days (Figure 4.1). Actigraphy uses a wrist accelerometer that produces a signal whenever movement is detected. Using data obtained from actigraphy, clinicians and researchers can identify periods of rest/sleep or activity, and determine total wake time, total sleep time, frequency of awakenings during the night and wake time after sleep onset (Morgenthaler *et al.,* 2007a). Sleep onset latency can also be discerned if actigraphs are used with an event monitor (i.e. the patient presses a button when he or she gets into bed). Generally, actigraphy is better at measuring sleep duration than identifying sleep onset. Since many persons follow different sleep-wake schedules during week, it is essential to monitor weekdays (i.e. schooldays or workdays) and weekends (i.e. non-schooldays and non-workdays). Occasionally, a psychiatric evaluation may be necessary to exclude depression as a cause for terminal insomnia. Other considerations for early morning awakenings include use of short-acting hypnotic agents for insomnia and ingestion of alcohol at bedtime. Awakening may occur during the night as the medication or substance is metabolized as determined by its dose and elimination half-life. Lastly, since rapid eye movement
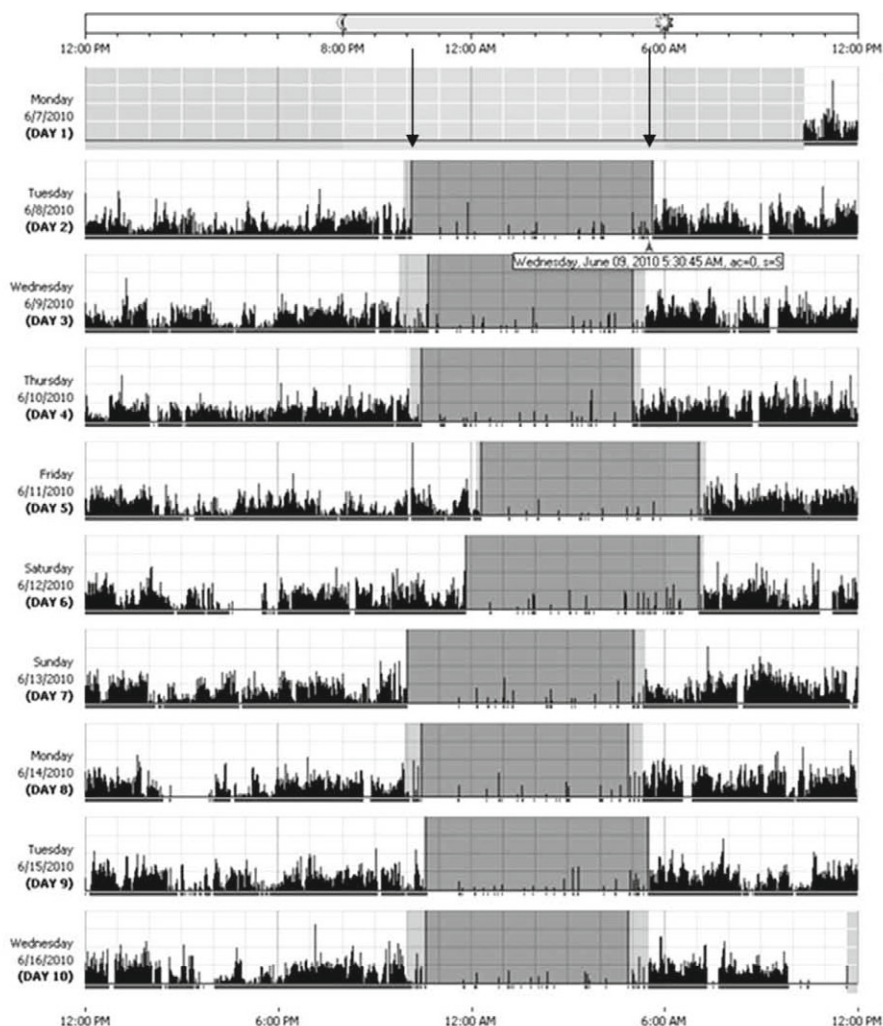
Figure 4.1. Actigram of a 25-year-old female without reported sleep complaints. The shaded area (between arrows) represents decreased movement (sleep). Note that the patient went to bed later on Friday and Saturday nights but awoke later in the morning on Saturday and Sunday.

sleep is more predominant during the latter part of sleep, both rapid eye movement(REM)-related obstructive sleep apnea and nightmare disorders can give rise to terminal insomnia.

PSG is not indicated for diagnosis. It is, however, important to realize that, if performed for other indications, sleep architecture may be altered by the underlying circadian misalignment. If PSG is recorded over the usual advanced sleep schedule, sleep latency, duration and quality are generally normal. In contrast, sleep onset latency is shortened and total sleep time is reduced if the sleep study is performed during conventional laboratory times since the patient will already be sleepy

by the time they arrive at the sleep laboratory and would tend to awaken earlier than the expected termination of the sleep study, respectively.

Therapy of ASPS involves a combination of phototherapy and chronotherapy (i.e. gradually delaying bedtimes and arising times until the desired sleep schedule is attained) (Morgenthaler *et al.,* 2007b). Phototherapy, which consists of early evening bright light exposure accompanied by early morning light restriction, should be timed to promote a phase delay in the sleep-wake rhythm. Contraindications to phototherapy include retinopathy, and photosensitivity. Caution should be exercised in patients with mania and migraine headaches. An ophthalmologic exam is recommended in patients with significant retinal and ocular disorders prior to initiating phototherapy. The timing, duration and intensity of light therapy should be individualized.

It is also essential to avoid excessive napping and increase activity during the day as well as optimize the bedroom environment for sleep during the night. Comorbidities that can disrupt sleep, such as nocturia, paroxysmal nocturnal dyspnea, pain syndromes and mood disorders, should be addressed. Timing of medications should take into account its effect on nighttime sleep quality and duration; for instance, patients should be advised not to take diuretics at bedtime. Finally, actigraphy can be used to monitor response to therapy.

4.2.2 Delayed sleep phase syndrome

DSPS is characterized by a habitual delayed bedtime (e.g. from 1 am to 6 am) and equally delayed arising time (e.g. from 10 am to 2 pm) (Sack *et al.,* 2007). Thus, the major nighttime sleep period regularly occurs later than a socially acceptable or preferred bedtime. Main clinical features include sleep-onset insomnia when sleep is attempted at more conventional and earlier bedtimes, and marked difficulty awakening in the morning that is occasionally associated with confusion as well as morning sleepiness. There is typically no difficulty in remaining asleep following the onset of sleep unless the patient has other underlying causes for sleep disturbance. Indeed, because most affected individuals tend to have some degree of sleep restriction (i.e. reduced total sleep time and decreased sleep efficiency), sleep duration is often normal, or even prolonged, if sleep is allowed to continue until spontaneous awakening during the preferred sleep-wake schedule; many patients describe 'catching up' on their sleep during non-school or non-work days when they are able to 'sleep in'.

This syndrome has an estimated prevalence of 0.1-0.2% in the general population (Schrader *et al.,* 1993) but accounts for 5-10% of cases of suspected chronic insomnia seen in sleep clinics (Weitzman *et al.,* 1981). Many persons with DSPD report a positive family history of the disorder, and an autosomal dominant pattern of inheritance has been described for certain patients.

Prevalence is highest among adolescents and young adults and DSPS affects both genders equally. Interestingly, most adolescent patients present for evaluation after a few weeks after school has started following their summer vacation. Having progressively delayed their sleep-wake schedules during the summer break from school, they then experience marked insomnia and daytime

sleepiness when they have to go to bed earlier in order to get sufficient time to sleep before they have to awaken early to get to school on time. The same problem may arise when they enter the workforce after college.

The delayed sleep-wake rhythms tend to persist if untreated; however, the degree of sleep delay may lessen with increasing age. In addition to sleep deprivation and habitual absence or tardiness for early work or school schedules, adverse consequences of DSPS include secondary conditioned insomnia and mood disorders. Individuals who are forced to go to bed earlier (e.g. children whose parents strictly enforce an early bedtime) or those who mistakenly believe that simply going to bed early will reverse their endogenous sleep-wake rhythms, often remain awake in bed for several hours and become anxious and frustrated, which are breeding grounds for the subsequent development of psychophysiologic or comorbid insomnia.

The proposed pathophysiology of DSPS is similar, but opposite, to that of ASPS: (a) a phase delay of the endogenous circadian pacemaker in relation to conventional sleep-wake schedules, coupled with (b) inability to phase advance in order to correct the disturbance. Contributory social and behavioral factors are equally important. Persons may be exposed to light until late in the night before they eventually fall asleep, and may also have minimal morning light exposure since they remain asleep in bed until late morning or early afternoon.

Evaluation of suspected DSPS starts with a thorough sleep history. Diagnosis is aided by sleep logs/diaries and actigraphy for at least 7 days, both of which show a regular pattern of late bedtimes and late waking times (Figure 4.2). Polysomnography is not indicated for the diagnosis of DSPS. Sleep architecture during PSG is often normal when the latter is recorded at habitually delayed sleep periods, but demonstrates prolonged sleep onset latency and reduced total sleep time when performed during desired sleep-wake times – i.e. patients undergoing testing are generally not sleepy when PSG recording is started and may sleep relatively briefly when the test is ended. The differential diagnosis of DSPS is extensive and includes many disorders associated with sleep-onset insomnia, such as idiopathic insomnia, psychophysiologic insomnia, poor sleep hygiene, environmental sleep disorders, and psychiatric conditions (mood and anxiety disorders).

Chronotherapy, phototherapy and melatonin administration are used to manage patients with problematic DSPS. Therapy may not be necessary for some individuals, who due to personal choice or occupational needs, may prefer to have a delayed sleep-wake schedule and describe no associated impairments in mood or functioning.

Chronotherapy may involve a progressive phase delay technique (bedtime and wake times are delayed by about 2-3 hrs each day on successive days until desired or conventional bedtime is reached) or progressive phase advancement (gradually advancing bedtimes by 30-60 minutes and waking times until desired schedule is attained) (Czeisler *et al.,* 1981). Progressive phase delay takes advantage of the patient's inherent ability to delay their bedtimes, but can disrupt a person's school or work schedules as it 'marches' the sleep-wake schedule around the clock over several days. A third technique, schedule shift protocol, consists of allowing the patient to follow
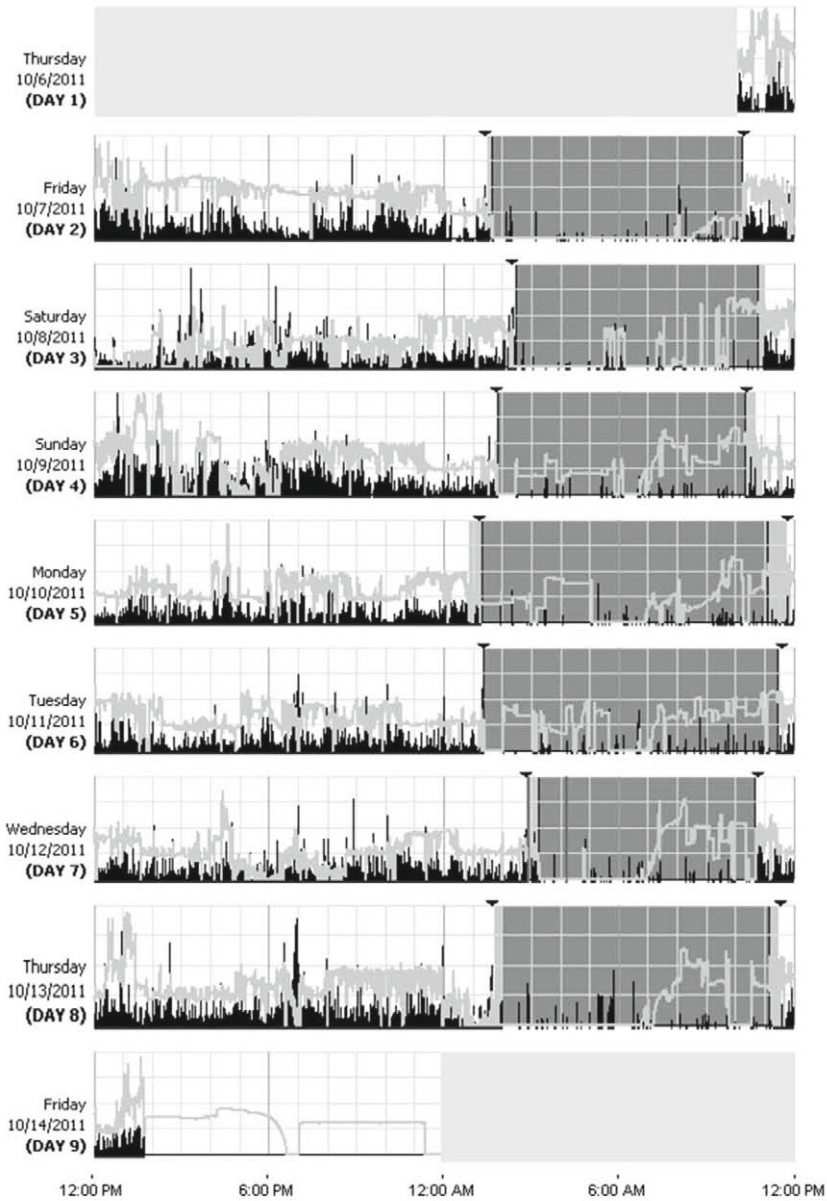
Figure 4.2. Actigram of a 14-year-old male who complained of excessive daytime sleepiness during the school year. This actigram represents his typical sleep/wake schedule during the summer break. He would usually fall asleep between 12 am and 2 am and awaken between 10 am and 12 pm.

the usual sleep schedule for six consecutive nights followed by a night of sleep deprivation. A 90-minute advance in sleep schedule is followed for the six subsequent days before the patient is again deprived of sleep for one night. This protocol is repeated until desired bedtime is attained. The one disadvantage to the schedule shift protocol relates to concerns regarding performance impairment and safety during the period following the sleep-deprived day.

Phototherapy consists of timed early morning exposure and evening avoidance of bright light. As in ASPS, the intensity, timing and duration of light exposure should be individualized. Light exposure for DSPS should be provided after CTmin since light exposure prior to CTmin could theoretically further phase delay circadian rhythms. Core body temperature is commonly at its nadir 2 hrs before habitual wake time. For instance, a high school student who regularly goes to sleep late at 3 am and wakes up at 11 am on weekends and during vacations, will have a CTmin at about 9 am. Therefore, phototherapy provided at the desired wake time of 6 am on schooldays (i.e. prior to CTmin), will be less effective or, worse, can potentially aggravate the condition.

Another useful therapy for DSPS is melatonin administered in the early-mid evening to help phase advance the sleep-wake cycle (Van Geijlswijk *et al.,* 2010). When combined with intermittent morning bright light exposure, melatonin administration can provide larger phase advancement than with phototherapy alone (Revell *et al.,* 2006). Actigraphy can be used to monitor response to therapy. Since there is a high risk of relapse, maintenance of the desired sleep-wake schedule once established is essential. In addition to proper sleep hygiene, patients should be counseled to maintain a regular sleep schedule throughout the week. Periodic therapy with timed light exposure or melatonin administration may be necessary if relapse is imminent.

4.2.3 Free running disorder

Freed of *zeitgebers*, the endogenous sleep wake rhythm, which have a periodicity of over 24 hrs, progressive delays by about 1 hr or more each day. Possible mechanisms for FRD include weakness of *zeitgebers*, decreased sensitivity to *zeitgebers*, or markedly prolonged circadian period beyond the range for external 24-hr entrainment.

Since the major sleep period 'marches' throughout the 24-hr day, affected individuals present with recurring insomnia or hypersomnia when the endogenous rhythm is 'out-of-phase' with the external world, alternating with complete, but brief, disappearance of symptoms when the internal and external rhythms are synchronized. Sleep duration is normal if patients are allowed to sleep *ad libitum*.

Free running disorder is rare in the general population, and most reported cases involve blind individuals who lack photic entrainment (Sack *et al.,* 1992). About 70% of blind individuals complain of chronic sleep-wake disturbances, and an estimated 40% have chronic, recurring and cyclical insomnia suggestive of FRD. Nonetheless, some blind persons are able to partially entrain to the environment using non-photic *zeitgebers*, such as regular social schedules, or photic cues using an intact circadian retinohypothalamic pathway. Aside from blind persons, FRD can also

be seen in individuals with severely schizoid or avoidant personality disorders, mental retardation or dementia. This disorder can start at any age.

Sleep history and sleep logs or actigraphy performed over several days are used to evaluate individuals with suspected FRD. Circadian phase markers, such as measurement of CTmin or salivary melatonin, may be useful if history, sleep diaries and actigraphy alone are insufficient to establish the diagnosis. Neurological evaluation to exclude any occult central nervous system pathology should be considered for sighted persons presenting with features of FRD.

Therapy should be individualized. Phototherapy with morning light exposure may be tried for patients with light perception. Strict regulation of the timing of bedtime, arising times, activities and meals as well as planned daytime napping may suffice in mild cases. Patients with more severe symptoms and functional impairment may benefit from evening administration of melatonin (Hack *et al.*, 2003; Sack *et al.*, 2000).

4.2.4 Irregular sleep wake rhythm

In ISWR, there is day-to-day variability in sleep and wake times due to absence of stable circadian sleep-wake rhythms. Insomnia, daytime sleepiness and/or cognitive impairment are common clinical features. Despite the inconsistent and unpredictable sleep and wake times throughout the day, the aggregate sleep time over a 24-hr period is typically near normal or normal for age.

Irregular sleep wake rhythm is believed to be rare in the general population. Onset of the disorder can occur at any age. It is most frequently seen in persons with severe brain dysfunction and affects both genders equally.

Diagnosis is aided by sleep logs and actigraphy performed over several days. Actigraphy can also be utilized to monitor response to therapy. Disorders that can present with irregular sleep wake schedules should be excluded; these include shift work, poor sleep hygiene, substance or alcohol abuse, caregiving responsibilities for children or adults with chronic illness, or environmental factors that can disturb sleep.

Therapy of ISWR starts with maintenance of regular schedules of sleep and waking as well a timed physical activity during the day. Phototherapy (daytime light exposure) and evening administration of melatonin may help stabilize sleep-wake rhythms.

4.3 Summary

Evaluation of CRSDs should include a thorough medical and sleep history, sleep logs or diaries, and actigraphy. Polysomnography is not indicated to diagnose CRSDs. Therapy consists of chronotherapy, phototherapy for ASPS, DSPS, FRD (in persons with light perception) and ISWR, and melatonin for DSPS, FRD and ISWR.

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Summary points

- The circadian system and the homeostatic regulation of sleep are interrelated. Age, sex, genetic predisposition and the environment influence circadian and sleep duration individual differences.
- *CLOCK* (circadian locomotor output cycles kaput) gene variants are associated with sleep duration and obesity in humans, and *CLOCK* mutant mice sleep shorter and show metabolic dysfunctions.
- Both the molecular components of the circadian clock and circadian misalignment are related to the aetiology of the metabolic syndrome.
- Unbiased genome-wide association studies for sleep duration identify genes involved in energy metabolism.
- *ABCC9* (ATP-binding cassette, sub-family C member 9) is functionally relevant for both sleep duration and symptoms of metabolic syndrome.
- Individual genetic predisposition, sleep habits, and its seasonality, may interact and contribute for an individual's susceptibility to obesity.

5. Gene variants associated with sleep duration: implications for metabolic dysfunction

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Abstract

Extremes in duration and (circadian) timing of sleep have been associated with adverse health, specifically with the symptomatology that characterises the metabolic syndrome. Several genes have been identified in model organisms to be involved in sleep regulation, many of which play also a role in metabolic dysfunction. Although the underlying mechanisms are not well known, homeostatic and circadian sleep regulation interactively influence energy metabolism. Environmental cues, such as time of year and amplitude of seasonal changes influence both sleep behaviour and energy metabolism, supporting the link between these two systems. Most of the hypotheses on the molecular mechanisms of human sleep regulation are derived from animal experiments. Genetic association studies have, however, also identified human genes that are potentially involved in the regulation of both sleep and (energy) metabolism, including those that are associated with sleep duration in the general populations. Some of these associations have been verified in animal experiments. Animal knockouts of these genes lead to the symptoms characteristic of the metabolic syndrome. Here we review these inherent aspects suggesting a link between homeostatic sleep regulation and metabolic dysfunction. These insights may be useful for identifying the molecular links between sleep and metabolism.

Keywords: metabolic dysfunction, CLOCK, ABCC9

Abbreviations

ABCC9	ATP-binding cassette, sub-family C member 9
BMAL1	Brain and muscle aryl hydrocarbon receptor nuclear translocator (ARNT)-like
BMI	Body mass index
CLOCK	Circadian locomotor output cycles kaput
CRY	Cryptochromes (a class of blue light-sensitive flavoproteins found in plants and animals; encoded by the genes CRY1 and CRY2)
DEC2	BHLHB3; Class E basic helix-loop-helix protein 41
DST	Daylight saving time
GWAS	Genome-wide association studies
K_{IR}	Inwardly rectifying potassium channels
PROK2	Prokineticin 2
REM sleep	Rapid eye movement sleep
SNP	Single nucleotide polymorphism
SUR	Sulfonylurea receptors (SUR1 and SUR2, subunits of the inward-rectifier potassium ion channels)

5.1 Introduction

Sleep duration and the circadian clock potentially play a key role in the regulation of energy metabolism, and may thus help to understand the etiology of metabolic syndromes (for review, see Huang *et al.*, 2011; Laposky *et al.*, 2008). Accumulating experimental and epidemiological evidence suggests that individuals who sleep longer or shorter than their physiological need are predisposed to gain weight (Nielsen *et al.,* 2011; Taheri and Thomas, 2008). To understand the mechanism underlying these relationships, we need more physiological and molecular research. In this chapter, we discuss the current state of genetic evidence and gene-environmental interaction that are thought to underlay the mechanisms that link sleep duration to metabolic dysfunction.

5.2 Sleep homeostasis vs. circadian system

Although sleep is a highly complex trait, it is characterised by two straightforward qualities: timing and duration, which are influenced by two physiological processes: homeostasis (how long have we been awake) and a circadian timing (Borbely, 1998). The latter refers to an endogenous clock that regulates a myriad of processes – from gene expression, physiology and metabolism to behaviour (including sleep) and cognitive performance. Circadian clocks in different individuals entrain specifically to environmental cycles (*zeitgebers*, e.g. light and darkness) – earlier or later within the day (so-called chronotypes; for review, see Allebrandt and Roenneberg, 2008). The underlying molecular mechanism that generates the *internal* day is thought to involve a transcriptional regulatory loop of so-called clock genes and their products (Roenneberg and

Merrow, 2005). Circadian rhythms are found in all phyla, from cyanobacteria to mammals (Roenneberg and Merrow, 2005) and species-specific clock genes have been identified in many model systems by reverse genetics. The function of clock genes not only concerns the generation of circadian rhythmicity, but also in controlling sleep homeostasis (Franken and Dijk, 2009). Sleep timing, sleep duration and even the temporal regulation of non-REM sleep may be altered when clock genes (e.g. neuronal PAS domain-containing protein 2, *BMAL1*, *CLOCK*, D site of albumin promoter (albumin D-box) binding protein) are knocked out in mice (note that D site of albumin promoter (albumin D-box) binding protein also regulates the expression of genes involved in gluconeogenesis and lipogenesis; for review, see Huang *et al.,* 2011).

Both sleep timing and duration depend on age and sex (Figure 5.1). Sleep shortens drastically (by ≈ 2 hrs) between childhood and the end of adolescence. From that age on (until about the age of menopause at 52), males sleep on average 15 min less than females (Allebrandt *et al.,* 2010). Sleep duration decreases steadily in both sexes from the end of adolescence (at around the age of 20) to the age of menopause in women; the sex-differences disappear at higher ages and sleep duration increases slightly (Figure 5.1a and b). The confounding influences of these systematic age and sex dependencies have to be either controlled for (i.e. normalised; used as co-variants) in epidemiological or genetic association studies. Large inter-individual differences remain even when sleep duration is normalised for age and sex (Allebrandt *et al.,* 2010), indicating that this phenotype is controlled by multiple genes (twin studies indicate a 40% heritability; Partinen *et al.,* 1983). A polygenic basis for sleep duration is also suggested by quantitative trait locus studies in mice and *Drosophila* (for review, see Allebrandt *et al.,* 2010).

5.3 Clock gene variants associated with sleep duration

Human chronotype is partly influenced by genetic factors known from animal experimentation (Roenneberg and Merrow, 2005). In humans, the mechanisms of the molecular clockwork remain hypothetical since the involved genes are predominantly based on sequence similarity with those in other animals. To characterise the relevance of mammalian clock genes for sleep timing and duration in humans, association studies of sleep duration with naturally occurring genetic variation in these genes have been conducted (for review, see Allebrandt and Roenneberg, 2008). The strongest evidences of such associations were found in specific families, e.g. a monogenic mutation in *PER2* was associated with advanced sleep phase syndrome (Jones *et al.,* 1999) and a mutation in the h*DEC2* (a regulator of CLOCK and BMAL1) gene with a shortening in sleep duration. The functional relevance of *DEC2* for sleep duration was confirmed in transgenic mice and *Drosophila* knockouts for the gene homolog (He *et al.,* 2009).

These studies were however primarily focused on specific families and rare gene variants. We recently systematically investigated the association of a set of high-density markers of 19 clock genes (Figure 5.2) with sleep duration (Allebrandt *et al.,* 2010). This was a two-stage design association study, involving populations from South Tyrol (discovery sample) and Estonia (confirmation sample). SNP markers were selected based on a linkage disequilibrium strategy,
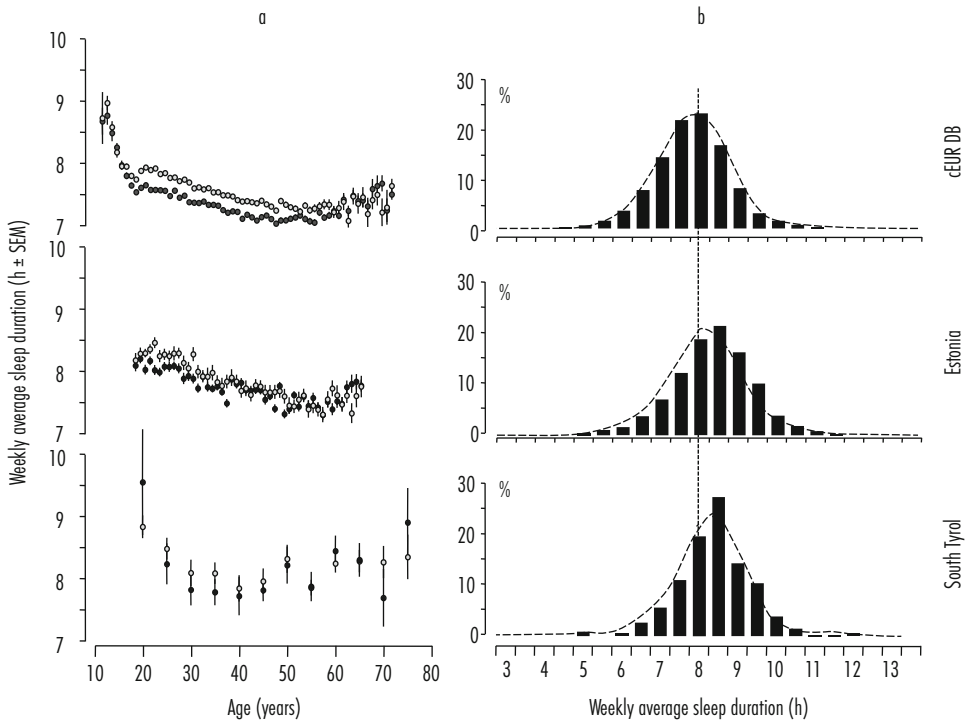
Figure 5.1. Sleep duration depends on age and sex. (a) On average, women (open circles) sleep longer than men (filled circles). The age-dependency of not-normalised averaged weekly sleep duration is plotted, separately for the genders, for a large Central European database (cEUR DB) (upper left panel) as well as for samples from Estonia (middle left panel) and South Tyrol, Italy (bottom left panel) sample on a 5-year basis. (b) The distributions of weekly average sleep duration in the different populations. The cEUR DB (upper right panel), Estonia (middle right panel), and South Tyrol (bottom right panel). The distributions of the raw data are drawn as stippled curve, and the distribution of the age and gender corrected data are drawn as bars. For orientation purposes, a vertical line is drawn through sleep duration of 8 hrs (Allebrandt *et al.,* 2010, copyright permission from *Biological Psychiatry*).

or on their possible relevance as non-synonymous or splicing region variants. In spite of the large variables set investigated, the top two most significant associations were located within the gene *CLOCK* – an essential transcription factor of the molecular circadian clock. The best signal in that study (rs12649507) co-segregates with a *CLOCK* variant (rs6843722) that has been associated with obesity in candidate genes studies (for review see Allebrandt *et al.,* 2010). Although obesity is known to correlate with sleep duration (Taheri and Thomas, 2008), we did not find an association of rs12649507 with BMI. This is not surprising because there were only extremely weak correlations between normalised BMI and normalised sleep duration in our samples (for review, see Allebrandt *et al.,* 2010).
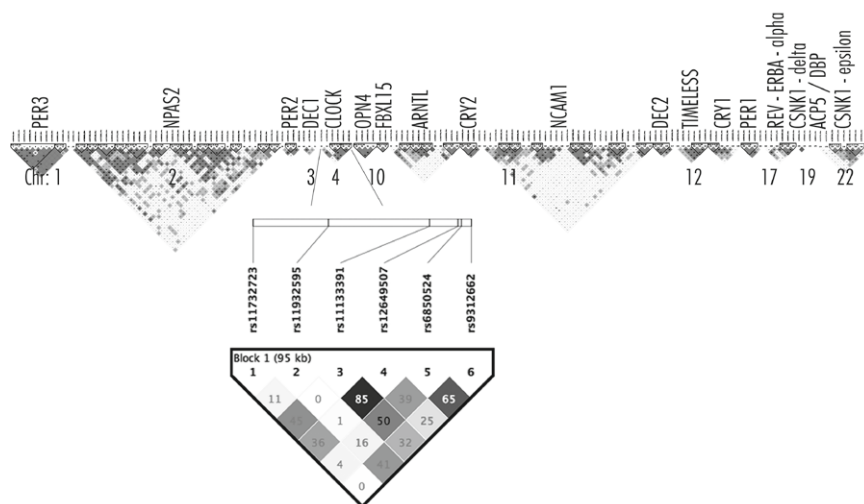
Figure 5.2. Candidate clock genes association study for sleep duration. Linkage disequilibrium structure (triangle plots) for all investigated single nucleotide polymorphism (SNP) markers (rs numbers below gene names). Dark diamonds indicate strong historical linkage disequilibrium (LD), D'-based haplotype boundaries, among SNPs. The amplified image is an r2 based triangle plot of the circadian locomotor output cycles kaput (CLOCK) gene with genotyped tags indicating, from black to white, complete to absent LD based on HapMap data (Allebrandt *et al.,* 2010, copyright permission from *Biological Psychiatry*).

NPAS = neuronal PAS domain-containing protein 2; PER = period; DEC = class E basic helix-loop-helix protein 41; OPN4 = melanopsin; FBXL15 = F-box and leucine-rich repeat protein 5; ARNTL = aryl hydrocarbon receptor nuclear translator-like (also known as BMAL1); CRY = cryptochromes; NCAM1 = neural cell adhesion molecule 1; REV-ERBA-alpha = also known as NR1D1 (nuclear receptor subfamily 1, group D, member 1; CSNK1 = casein kinase I isoform; ACP5 = acid phosphatase 5; DBP = D site of albumin promotor (albumin D-box) binding protein; TIMELESS = encodes TIM, an essential protein that regulates circadian rhythms

CLOCK encodes a basic helix-loop-helix transcription factor, which forms a complex with the protein BMAL1. This heterodimer is the activating component of a negative feedback-loop that is critically involved in circadian rhythm generation at the cellular/molecular level (Borbely, 1998). In addition to its central role in the circadian clock, this gene plays a role in sleep regulation. *CLOCK* gene polymorphisms have been associated with insomnia, an apparent inability to consolidate sleep (*T3111C*; rs1801260 located in the 3' flanking region) and with temporal sleep preferences, so-called Morningness and Eveningness (for review, see Allebrandt and Roenneberg, 2008). Deletion of *CLOCK's* exon 19 (due to a point mutation) shortens both the duration of sleep (by 1-2 hrs) and that of REM-phases in mice (for review, see Laposky *et al.,* 2008). These mutants show also changes in energy (decreased appetite along with symptoms of the metabolic syndrome:, obesity, hyperleptinemia, hyperlipidemia, hyperglycemia and insufficient compensatory insulin production; Turek *et al.,* 2005). Notably, these traits are associated with extremes of sleep duration (Taheri and Thomas, 2008).

5.4 *CLOCK* and the circadian system: relevance for the energy metabolism

Genome-wide association studies for obesity and metabolic syndrome also revealed associations of *CLOCK* variants (rs4864548/rs3736544/rs1801260) with these traits (for review, see Huang *et al.,* 2011). Additionally, a *CLOCK* coding variant (*T3111C*) associates with Ghrelin levels, a hormone involved in the regulating feeding behaviour (Garaulet *et al.,* 2011).

Consistently with these findings, *CLOCK* expression within human adipocytes correlates with obesity (Wu *et al.,* 2009). Note, that the circadian clock also modulates levels of glucose, insulin, and leptin, as shown in humans (Scheer *et al.,* 2009) and in clock genes knockout mice. *CLOCK* mutant mice develop hypoinsulinemic hyperglycemia and show loss of vascular adaptation with predisposition to thrombosis (for review, see Laposky *et al.,* 2008). Genetically obese mice (homozygotes lacking the *ob* gene) show disrupted circadian rhythms, and their obesity is exacerbated when additionally mutated for *CLOCK* (for review see Huang *et al.,* 2011). Thus, *CLOCK* clearly plays a role on metabolic regulation. A relation of *CLOCK* to a number of genes involved in disease and metabolism is indicated in a vast number of scientific publications; a diagram of these relationships is presented in Figure 5.3.

Other knockouts of clock genes indicate tissue specific functions in the regulation of gluconeogenesis: hepatic gluconeogenesis is for example increased in *Cry*-knockout mice (related to up-regulation of cAMP signalling) and is decreased when *Bmal1* is knocked out in the mouse liver (for review, see Huang *et al.,* 2011). Supporting these findings, GWAS for fasting glucose levels revealed associations of this trait with *CRY2* and *BMAL1* gene variants (for review, see Huang *et al.,* 2011).

Beyond these genetic studies, epidemiological observations relate circadian desynchronisation (circadian misalignment) to adverse health outcomes, such as sleep disorders, depression (Wulff *et al.,* 2010), and metabolic syndrome (Scheer *et al.,* 2009). Associations between sleep, circadian timing and metabolic pathologies have long been a concern for shift workers. The situation, where people have to be active and try to sleep outside the appropriate circadian times, has been simulated in carefully controlled laboratory studies called 'forced desynchrony'. These simulations result in an imbalanced glucose metabolism that normally is associated with metabolic syndrome or type II diabetes (Scheer *et al.,* 2009). Similarly, diabetic patients exhibit dampened amplitude of rhythms of glucose tolerance and insulin secretion (Boden *et al.,* 1999).

As an explanation for these associations, one could hypothesise that environmental influences may also modify CLOCK function either as a transcription factor or as a histone acetyltransferase, and in turn have an effect on sleep duration and/or metabolism. Whether through epigenetics, gene-gene interaction or isolated polymorphisms, there is a possible influence of CLOCK on epidemiological variation on sleep duration and metabolic dysfunction (Allebrandt *et al.,* 2010).
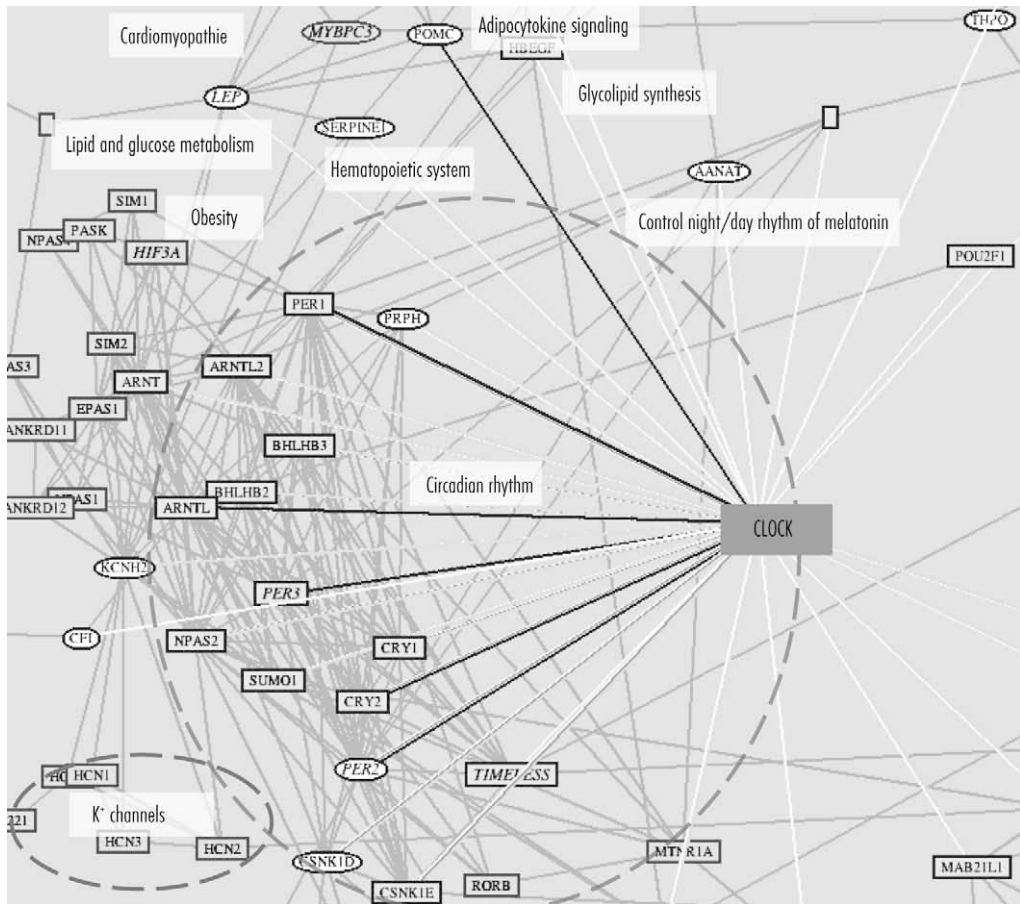
Figure 5.3. CLOCK genetic interaction network. Oval nodes represent genes associated with diseases, and rectangular nodes represent other genes. The edges represent the strength of the link between pairs of genes. Short edges link genes sharing a large number of biological keywords. The diseases or metabolic process that these genes (dashed areas) are involved with are highlighted in the white rectangles (generated with SNPs 3D).

5.5 GWAS: an unbiased approach to identify sleep duration genes

Sleep duration is a polygenetic trait, so that other genes (beyond clock genes) are expected to play a critical role in shaping the phenotype distribution of this trait – characteristic of polygenic inheritance. Genome-wide association is an unbiased approach to detect such associations. A small-scale genome-wide scan (Gottlieb *et al.,* 2007) identified a linkage peak in the h*PROK2* gene that is associated with sleep duration. h*PROK2* is controlled by the CLOCK-BMAL1 complex, again reflecting a link to the circadian system, and *PROK2* mutant mice showed disrupted non-REM sleep (Franken *et al.,* 2007). To cover a larger proportion of the human genome, we conducted GWA studies with a dense set of markers across 7 European populations (Allebrandt *et al.,* 2011). The meta-analysis of these discovery cohorts (4,251 subjects) revealed a genome-wide

significant signal in the *ABCC9* (ATP-binding cassette, sub-family C, member 9) locus, which encodes a sulfonylurea receptor. Individuals who had two copies of one common variant of the gene *ABCC9* generally slept significantly shorter on work-free days than subjects with two copies of the other version, which explained ≈5% of the variation in sleep duration.

To investigate the functional relevance of SUR2 for sleep duration, we knocked down the expression of its *Drosophila* homologue (d*Sur*) in the flies' nervous system (both central and peripheral; Figure 5.4). *Drosophila* has a single invertebrate ATP-binding SUR protein (d*Sur*), which is homologous to SUR2 (for review, see Allebrandt *et al.,* 2011). Unlike humans, flies are active predominantly around dawn and dusk and show two large sleep episodes, one during the day and one at night. Knock-down of d*Sur* dramatically reduced night-sleep, particularly during the first half of the dark period, but had little effect on the flies' day-sleep. Other potassium channel regulatory proteins, encoded by *Shaker, Hyperkinetic* and *Sleepless*, have been shown to influence sleep duration in *Drosophila*. Consistently with it, the results of our GWAS also supports the role of *Hyperkinetic* in modulating sleep duration in humans, as its human homologue, voltage-gated potassium channel subunit beta-1, was the second best associated gene in our meta-analysis (Allebrandt *et al.,* 2011). Additionally, K+ channels activity is enhanced when nicotinic acetylcholine receptors are blocked in the rat hypothalamus, and one of the nicotinic acetylcholine receptors genes (acetylcholine receptor subunit delta expressed in muscle tissue) was the third best ranking gene in the GWAS meta-analysis (for review see Allebrandt *et al.,* 2011). Several genes ranking among the best associations in our GWAS are related to energy metabolism (an overview of the 10 best ranking locus and their function can be found in Figure 5.2, Allebrandt *et al.* (2011)).

In relation to clock genes, casein kinase I isoform alpha, recently characterised as a clock regulator kinase (CK1α), showed the best associations (*P*<0.001), among 19 clock gene homologs, in the meta-analysis of our GWAS (Allebrandt *et al.,* 2011). Our results also indicate that (1) common variants having a small contribution for sleep duration – such as *CLOCK* gene variants (Allebrandt *et al.,* 2010) may have a significant effect only in combination with other variants; and that (2) single rare variants with large effects, e.g. *DEC2* (He *et al.,* 2009), will not explain the variation of sleep duration in general populations, which should rather be modulated by variants from several *loci*.

5.6 K$_{ATP}$ channels, sleep duration and metabolism

In vertebrates, *ABCC9* is expressed in various tissues (in mammals mostly in heart, skeletal muscle, adipose tissue, ovary, brain, tongue, and pancreatic islets) and has various splice isoforms, indicating its functional diversity and genetic complexity (for review, see Allebrandt *et al.,* 2011). SUR2 is a pore-forming subunit of ATP-sensitive potassium channels (K$_{ATP}$), known to be involved in energy metabolism (Akrouh *et al.,* 2009). SUR2A/K$_{IR}$6.2 membrane pores regulate the duration of action potentials in the heart, while SUR2B/K$_{IR}$6.1 pores regulate action potential duration and vasodilatation in vascular smooth muscle, depending on the state of intracellular
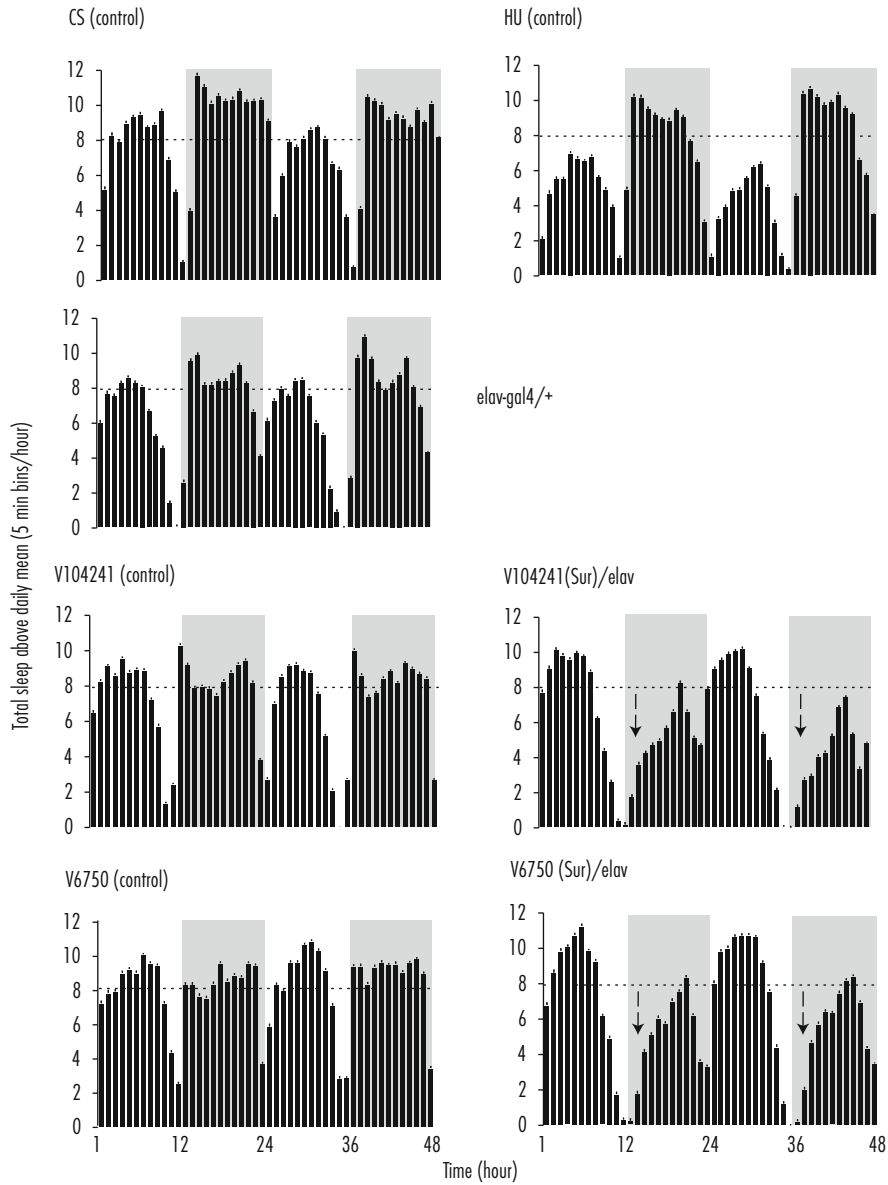
Figure 5.4. ABCC9 functional study in Drosophila. Pan-neuronal knockdown of *dSur* in *Drosophila* decreases night sleep duration. *elav-gal4* was crossed to each of two independent *UAS-Sur* RNAi lines (*V104241* and *V6750*). Plots of circadian immobility (> daily mean, in 5 min bins) of experimental and control males in 12:12 hr light/dark cycles over 2 days. Experimental flies show reduced sleep (defined as 5 min of immobility) in the first half of the night (see arrows *V104241(Sur)/elav* and *V6750(SUR)/elav*), compared to corresponding controls for the dark phase; gray background and dashed threshold line), while rest duration in the light period was similar among cases and controls. Sleep bouts in experimental flies were not significantly nor shorter in length nor more numerous than for control flies (Allebrandt *et al.,* 2011, copyright permission from *Molecular Psychiatry*).

ATP and glucose metabolism in voluntary striated muscle (Inagaki *et al.,* 1996). The functional relationships of these channel subunits suggest a higher order regulation that may have driven the preservation of their genomic co-localisation in the vertebrate lineage.

The SUR2 protein structure suggests a role as the drug-binding, channel-modulating subunit of extra-pancreatic K_{ATP} channels. Sulfonylureas are used for the treatment of diabetes, as they help to reduce blood glucose levels by closing the K_{ATP} channels, leading to an increase in insulin secretion. SUR2 is indeed shown to be involved with the development of human cardio-pathologies and diabetes (Akrouh *et al.,* 2009). The function of *ABCC9* is therefore connected to several disease and metabolic processes pathways (Figure 5.5).

In the brain, K_{ATP} channel action potentials mediate the state of cortical arousal modulated by neurones involved in slow-wave oscillations (during deep sleep), via a $K_{IR}6.2$ subunit. High glucose levels induce a significant decrease in the $K_{IR}6.2$ mRNA level, reversible by lower glucose concentration (for review, see Allebrandt *et al.,* 2011). Activation of hypothalamic $K_{IR}6.2$/SUR1 channels restrains hepatic gluconeogenesis (generation of glucose), while inhibition of Kir6.2/SUR-2B channels in the ventromedial hypothalamus are indicated to amplify the counter regulatory responses to acute hypoglycemia (McCrimmon *et al.,* 2005), providing a link between the CNS, liver metabolism and the development of diabetic hyperglycaemia.
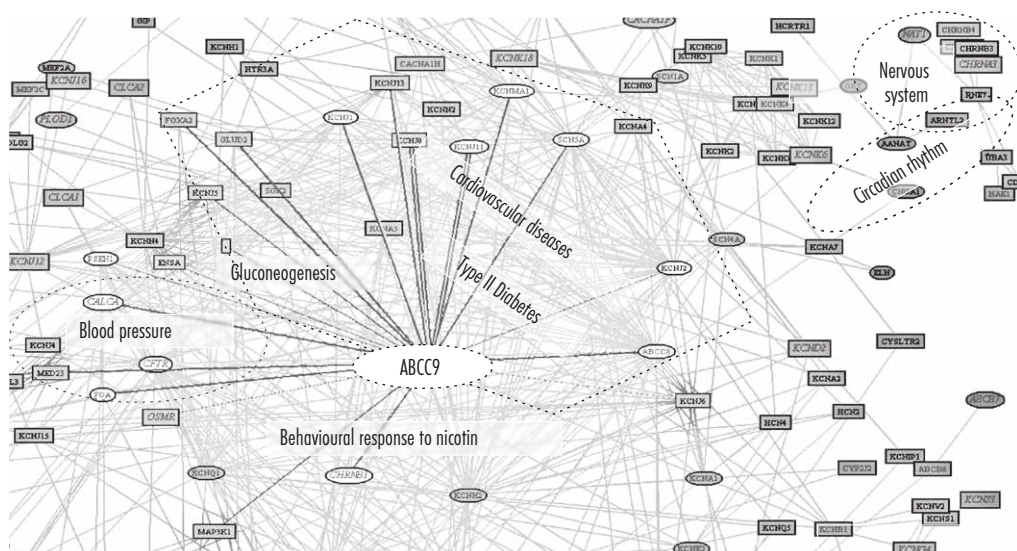
Figure 5.5. ABCC9 genetic interaction network. Oval nodes represent genes associated with diseases, and rectangular nodes represent other genes. The edges represent the strength of the link between pairs of genes. Short edges link genes sharing a large number of biological keywords. The diseases or metabolic process that these genes (dashed areas) are involved with are highlighted in the white rectangles (generated with SNPs 3D) (Allebrandt *et al.,* 2011, copyright permission from *Molecular Psychiatry*).

In contrast, orexin neurones, which innervate the arousal system in the brain helping to promote and sustain wakefulness, express $K_{IR}6.1/SUR1$ channels (for review, see Allebrandt *et al.*, 2011). Unlike the hunger-induced arousal mechanism (i.e. under glucose deprivation), K_{ATP} channels mediate hyperpolarisation of orexin neurons, thereby promoting sleep and exerting a neuro-protective mechanism during severe energy depletion (Parsons and Hirasawa, 2010). In this sense, non-functional K_{ATP} channels in these neurons could prolong wakefulness during energy depletion, as indicated by patch clamping of rat brain slices treated with K_{ATP} blockers in the absence of glucose (Parsons and Hirasawa, 2010). This supports an important role of K_{ATP} channels in balancing adaptive response to stress and the metabolic resources to ensure survival. Additionally, K_{ATP} channels are indicated to mediate the action of leptin on the regulation of food intake and body weight. Leptin activates these channels, inhibiting insulin secretion, thus promoting hyperglycaemia (Ashcroft and Gribble, 1999).

Moreover, ATP-sensitive potassium channels are indicated to be involved in the proliferation and differentiation of rat pre-adipocytes by changing the expression of cyclin-dependent kinase inhibitor 1A, cyclin-dependent kinase inhibitor 1B and leptin (Wang *et al.*, 2009). Leptin modulation of K_{ATP} channels, both centrally and peripherally, may form an integral part of the molecular machinery that maintains central and peripheral homeostasis of body weight and energy balance. Knockout mice for the *ABCC9* gene homolog show enhanced insulin-stimulated glucose uptake in the skeletal muscle (Chutkow *et al.*, 2001), suggesting the involvement of this gene with the aetiology of type II diabetes. The relevance of this locus for sleep duration regulation has therefore implications for dissecting the relationships between sleep duration, BMI, hypertension and disease.

5.7 Sleep duration, the circadian system and obesity: gene x environment interaction?

When circadian rhythms are investigated under constant condition, their endogenous periods often deviate from 24 hrs. Under natural conditions, circadian clocks are normally entrained by environmental signals (*zeitgebers*), predominantly by light. Photoperiod (i.e. season), which directly influences the circadian system by delaying or advancing phase of entrainment (chronotype), can also indirectly influence sleep duration (Kantermann *et al.*, 2007). Abrupt changes in social times, such as jetlag or daylight saving time transitions, interfere with the seasonal adaptation of sleep and its entrained phase, resulting in circadian misalignment and sleep deprivation (Kantermann *et al.*, 2007). Beyond the sleep/wake behaviour, body weight and mood are subjected to seasonal variation, which depends on the individual genetic predisposition as indicated by the heritability of this phenotype in families (Mikulecky *et al.*, 2004; Rajajarvi *et al.*, 2010). Light plays a crucial role entrainment of the circadian clock; day length (photoperiod) depends on time of year and the amplitude of its seasonal changes on latitude. These geographical specificities of light could be relevant in adaptation processes strengthening or weakening the impact of components within the circadian network. Latitudinal clines have been show for human reproduction (Roenneberg and Aschoff, 1990). In *Drosophila*, genetic geographic variations

between photoperiodic diapauses and the circadian eclosion rhythm have also been observed (for review, see Allebrandt and Roenneberg, 2008). In addition, synchronisation of circadian clocks to natural light-dark cycles is challenged at very high latitudes due to the extreme photoperiods. Therefore, a relationship between an adaptive circadian system and fitness is likely.

Photoperiod influences the circadian metabolism (i.e. clock genes expression) and modulates both sleep timing and duration (for review, see Allebrandt *et al.,* 2011; Kantermann *et al.,* 2007). Beyond the interactions between photoperiod and phase of entrainment (chronotype), the average sleep duration is altered during DST (Kantermann *et al.,* 2007). DST advances the social clock (i.e. work simply starts an hour earlier), increasing the discrepancy between social and the circadian timing, a phenomenon called *social jetlag*. Social jetlag and the resulting sleep deprivation are obviously more pronounced in late than in early types, and late types have greater difficulties to adjust to the DST changes than early types (Kantermann *et al.,* 2007).

Within a gene x environment context, genetic variation associated with sleep duration *versus* deviations of the individual sleep physiological needs could contribute to the individual susceptibility to obesity (Figure 5.6). Therefore, a genetic predisposition may represent the metabolic fitness to compensate from variations in sleep duration, which can lead to obesity depending on the individual sleep need. This would explain the discrepancies observed across studies investigating epidemiological associations of BMI and sleep duration. For instance, a recent study in twins shows shorter sleep duration in association with increased BMI and with increased genetic influences on BMI, suggesting that shorter sleep duration increases the genetic risks for high body weight (Watson *et al.,* 2010). The authors of this study imply that sleep curtailment provides a permissive environment for the expression of pro-obesity genes. In summary these observations show that, understanding the underlying mechanisms, connecting sleep and its seasonality to energy metabolism will be crucial to understand the link between sleep behaviour and obesity.
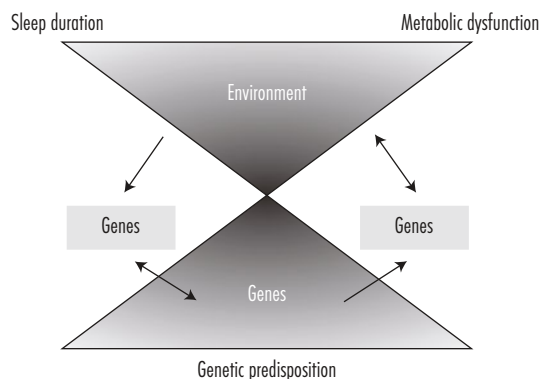
Figure 5.6. Sleep habits, individual genetic predisposition and environmental cues may interact and contribute for the individual susceptibility to metabolic dysfunction.

5.8 Concluding remarks

Individual genetic predisposition, sleep habits, and its seasonality, may interact and contribute for the individual susceptibility to obesity. Understanding the molecular link between sleep and metabolic dysfunction in humans will open avenues to improve individual treatment and prevention strategies. The characterisation of new genes and polymorphisms influencing sleep duration and the circadian phenotype will also strengthen *in vitro* functional studies investigating the molecular mechanisms controlling sleep homeostasis and the period of free running rhythms in humans. Finally, the insights into the genetics behind sleep duration and circadian phenotype should increase awareness about an individual's predisposition, and may consequently also lead to political changes facilitating more appropriate, flexible, or individualised social schedules (e.g. in school and work) or the abolishment of DST.

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Fasting, eating and sleep

Summary points

- Recent studies show that food intake is increased by acute sleep deprivation in humans.
- An archaic phylogenetic phenomenon, dependent on the length of day and night and mediated by melatonin secretion, might explain the relationship between the length of sleep and food intake.

6. Partial sleep deprivation and food intake in men

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Abstract

Does lack of sleep lead to obesity? Many studies show that in Western countries the duration of sleep has decreased in recent years. Epidemiological approaches have shown a link between short sleep duration and increased body mass index, but these studies did not identify that this link is causal and which mechanisms are involved. Experimental studies may help in that matter. Some of the metabolic effects of sleep deprivation in humans and in animals are reviewed. Then the results of a recent paper are given, which show that food intake is increased by acute sleep deprivation in humans and discussed in regards with the different hypothesis about the mechanisms involved. Finally, the increase of food intake during restricted sleep might be an archaic phylogenetic phenomenon which is still present and active in humans. This phenomenon could be the same as the seasonal variations in sleep and food intake according to the length of day and night in animals and could be mediated by melatonin secretion.

Keywords: obesity, suprachiasmatic nucleus, leptin, ghrelin, melatonin

Abbreviations

BMI   Body mass index
SDS   Sleep deprivation session

6.1 Background

Does lack of sleep lead to obesity? Many studies show that in Western countries the duration of sleep has decreased in recent years. For example, in the United States, people sleep on average two hours less than they did in 1960 and, in Japan the figure is three-quarters of an hour less. In France, according to a survey conducted in 2009 on 1000 people, one person in three aged 18 to 55 years sleeps for less than 6 hrs per 24 hrs. In parallel, the proportion of obese people worldwide has doubled in less than 30 years and the number of people with metabolic diseases such as diabetes has increased rapidly.

6.2 Epidemiological approaches

Currently, no fewer than sixty-five epidemiological studies (transversal and longitudinal) have been conducted in different countries and on large populations to evaluate the relationship between sleep duration and overweight or obesity (several reviews have been written, e.g. Gangwisch, 2009 and Knutson, 2010). Almost all of these studies have shown a link between short sleep duration (usually less than 6 hrs per night for adults and less than 10 hrs for children) and increased body mass index (the biggest individuals tended to sleep the least). This relationship was confirmed by two recent meta-analyses (Cappuccio *et al.*, 2008; Chen *et al.*, 2008). Note that several epidemiological studies also observed an association between short sleep duration and an increased risk of type-2 diabetes, a condition that occurs when the body has become resistant to insulin. Moreover, the risk of overweight in relation to the duration of sleep is not linear; it is a U-shaped curve [overweight individuals may be long or short sleepers (e.g. Patel *et al.*, 2004). Finally, children are much more sensitive than adults to the effects of sleep deprivation (e.g. Danielsen *et al.*, 2010).

Epidemiological studies do not say whether the weight/sleep-duration correlations neither result from a chance association arising from the same mechanism (confounder), nor do they identify the 'cause or the consequence' or understand the mechanisms involved. Regarding the latter, decreased sleep duration may increase food intake or intake duration, decrease energy expenditure or lead to a combination of these mechanisms. Experimental studies may elucidate the mechanisms involved.

6.3 Experimental studies

6.3.1 Metabolic effects of sleep deprivation in humans

The first experimental study on the metabolic effect of sleep deprivation in humans was published in 1999 (Spiegel *et al.*, 1999). Eleven healthy normal-weight men aged twenty years and without sleep disorders were followed for sixteen consecutive nights in a laboratory. During the first three nights, the volunteers were allowed to sleep 8 hrs. For the following six nights, they were subjected to partial sleep deprivation since they could sleep only 4 hrs. The following seven nights, they could spend 12 hrs in bed. All received the same meals. Results showed that after six nights of 4 hrs of sleep, the participants had impaired glucose tolerance and an increase in plasma cortisol levels in the late evening (by decreased sensitivity to insulin?). Therefore, the decrease in sleep duration was able to induce metabolic disturbances (reversible during the recovery period). In 2004, the same laboratory (Spiegel *et al.,* 2004) measured plasma concentrations of leptin (a satiety hormone mainly produced by adipose tissue) and ghrelin (an orexigenic hormone predominantly secreted by gastric cells) in twelve young healthy adults aged twenty years. Participants were allowed to sleep two nights of 10 hrs then two nights of 4 hrs. In both situations, subjects' physical activity was similar and they were fed by glucose infusions in order to receive exactly the same amount of calories (otherwise the changes in leptin and ghrelin could not be interpreted). After two nights of sleep restriction, leptin levels decreased by 18% and ghrelin levels increased by 28%. In addition, the hunger sensation increased by more than 20% and the desire for calorie-rich foods increased. Consequently, the lack of sleep had a positive impact on appetite and on two hormones that control this sensation. After these studies, many others confirmed that sleep deprivation could modify ghrelin and leptin levels.

6.3.2 Sleep deprivation in animals

In rats, there is an almost constant increase in food intake after acute or chronic sleep deprivation. However, here it is generally associated with weight loss, which is essentially linked to the activation of the adrenergic system due to stress resulting in increased energy expenditure. Furthermore, it has also been noted an increase in plasma ghrelin levels and food intake in rats deprived of sleep for 5 hrs and a decrease in plasma leptin concentrations after chronic sleep deprivation.

6.3.3 Food intake is increased by acute sleep deprivation in humans

In humans, studies that examined energy intake in relation to sleep deprivation are scarce. Some provide indirect arguments: habitual short-sleepers eat more often than long-sleepers (Hicks *et al.*, 1986), nibble more, use condiments in excess, have erratic food intake and consume fewer vegetables (Imaki *et al.*, 2002; Ohida *et al.*, 2001). Other studies showed that sleep deprivation increases the appetite (Schmid *et al.*, 2008; Spiegel *et al.*, 2004). In line with this, our group has recently observed a direct relationship between sleep deprivation and increased food intake (Brondel *et al.*, 2010).

Our study was conducted in 12 healthy young (22±3 y) men with normal bodyweight (BMI: 22.3±1.8 kg/m^2) and a regular sleep-wake rhythm (about 7.5-8 hr sleep/night). After a 48 hr period of observation at home (to assess physical activity, spontaneous food intake and sleep patterns), the subjects participated in two randomized 48 hr-experimental sessions (Figure 6.1).

During each session there was a control period of 8 hrs (in order to put the subjects in the same experimental conditions with respect to their physical activity and food intake), followed by the sleep period which lasted either 4 hrs (2 am to 6 am), i.e. the SDS or 8 hrs (midnight to 8 am), i.e. the NDS and then a 24 hr observation period (Figure 6.1). During this observation period, the subjects had access to a fixed breakfast ((B) they could only vary the amount ingested), a semi-fixed lunch ((L) buffet composed of 20 foods), a free afternoon snack (C) and a free dinner (D). The food intake in these four meals was measured. Olfactory liking for four foods and wanting for six other foods were evaluated before and after lunch. Hunger, sleepiness and the motivation to engage in physical activity were assessed every 1.5 hrs. Finally, subjects' physical activity was continuously recorded by an actimeter.

After the night of sleep deprivation, we observed an increase in appetite before both breakfast and dinner ($P<0.001$ and $P<0.05$, Figure 6.2), which led to an increase in food intake during these meals ($P<0.01$ and $P<0.001$, Figure 6.3). Consequently, participants consumed 560±620 kcal more (+22%, $P<0.01$) after the 4 hr-sleep night than after the night with 8 hr sleep with a 99% higher
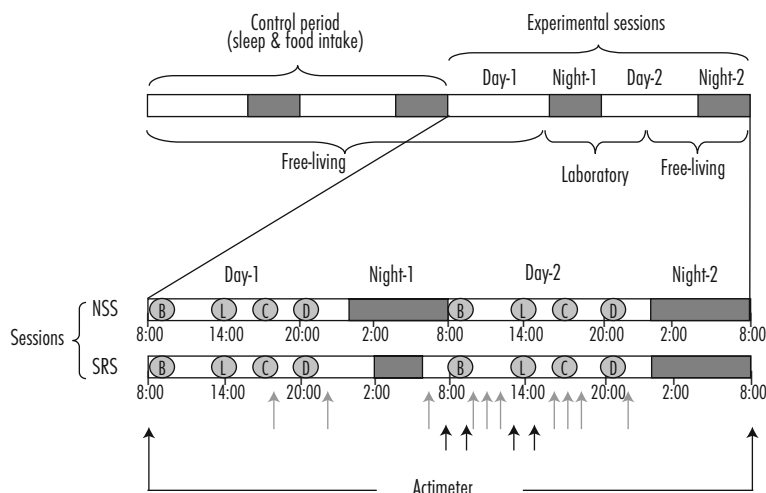
Figure 6.1. Timing of the experiment. Twelve subjects were recorded during (1) a control period of 48 hrs before the first session, then (2) a normal sleep session and (3) a SDS. For these two experimental sessions, (normal sleep session and SDS) the following parameters were evaluated: energy intake (at breakfast – B, Lunch – L, afternoon snack – C and dinner – D); hunger, pleasantness for the foods, sleepiness and 'motivation to engage in physical activity' (gray arrows); 'olfactory liking' for 4 foods and 'wanting' 6 other foods (black arrows); physical activity by actimeter (reprinted from Brondel *et al.,* 2010, with permission from the American Society for Nutrition).
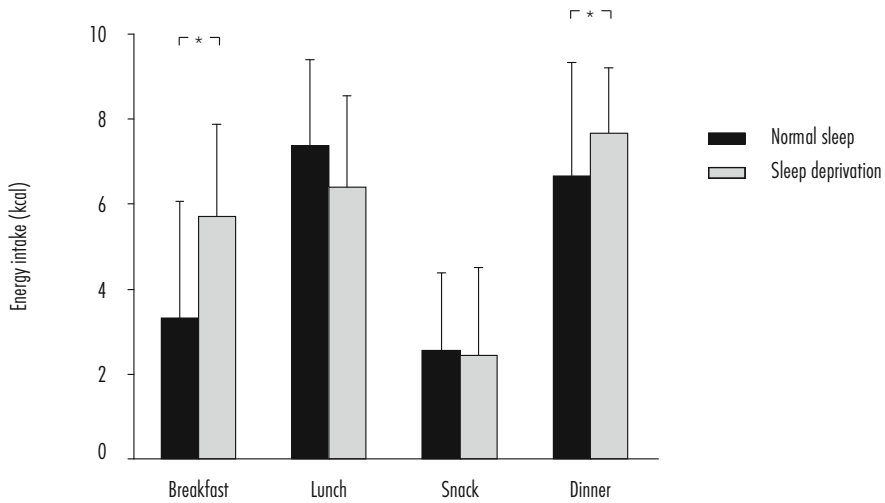
Figure 6.2. Pre-prandial hunger ratings after the normal/deprived sleep. Values ± SD were measured using 10 cm visual analogue scales. Paired t-tests indicate significant differences (*$P<0.05$) between the two sessions.
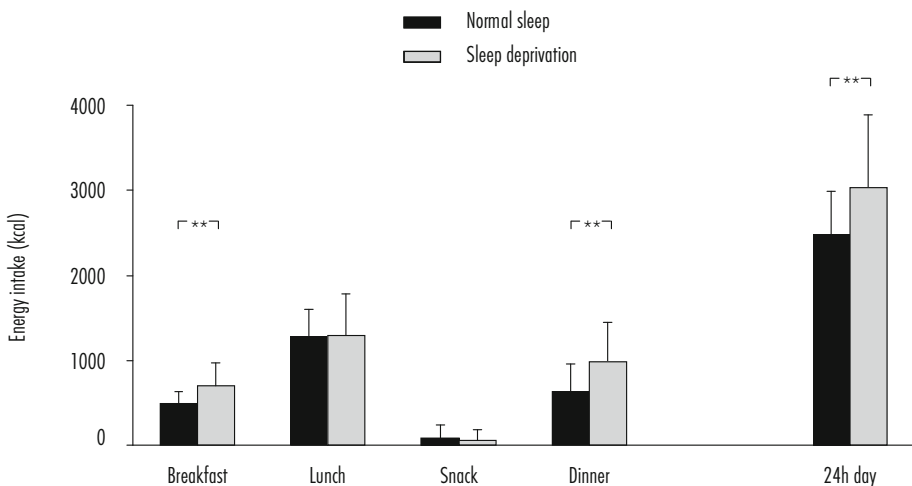
Figure 6.3. Energy intake at breakfast, lunch, afternoon snack and dinner after a normal night (Normal sleep) and after a night of partial sleep deprivation (Sleep deprivation). Values are means ± SD. Paired t-tests indicate significant differences (**$P<0.01$) between the two sessions.

consumption of fat during dinner ($P<0.001$). Furthermore, and although the desire to sleep was higher after the 4 hr-sleep night ($P<0.001$), subjects had a slight increase in their physical activity (2%, 50±50 kcal, $P>0.01$). During the 24 hrs following the normal/deprived sleep, according to the calculations of energy expenditure from the actimeters, subjects were nearly at equilibrium in terms of energy balance in the normal sleep session but in a state of positive energy balance in

the deprived sleep session (Table 6.1). This study thus highlights the fact that in the short-term, sleep deprivation may increase food intake and may consequently be a risk factor for becoming overweight or obese.

Our results are not consistent with those of two studies, probably due to methodological differences. In the first, Schmid *et al.* (2009) studied fifteen men with normal bodyweight for two nights of about 4 hr sleep and two nights of about 8¼ hr sleep. Spontaneous food intake, plasma leptin and ghrelin levels as well as energy expenditure related to physical activity (by actimetry) were measured. Food intake and hormonal changes were similar in the two situations although fatty food intake was higher after sleep restriction (*P*<0.05). Physical activity was reduced (*P*<0.01) after sleep deprivation. Analysis of the results revealed that subjects were in a positive energy balance in both sleep situations (≈ 60% according to the authors), even in the situation of

Table 6.1. Energy intake, macronutrient composition (% energy) of the foods consumed (A) and estimated energy expenditure (B) after a normal night (Normal-sleep session) and after a night of partial sleep deprivation (Sleep-restriction session).

A

	Normal-sleep session				Sleep-restriction session			
Energy intake and macronutrient composition								
	energy (kcal)	CHO (%)	fat (%)	proteins (%)	energy (kcal)	CHO (%)	fat (%)	proteins (%)
Breakfast	485±149	62±5	33±4	5±1	703±262**	61±3	34±3	5±1
Lunch	1,279±328	45±7	40±5	15±3	1,292±484	44±8	41±7	15±3
Afternoon	85±155	65±28	23±22	11±9	61±121	83±15	5±9	12±3
Dinner	630±320	42±11	37±14	21±9	982±470**	35±12	48±13*	17±5
Total	2,478±512	48±6	38±6	14±3	3,037±853**	45±7	41±6*	13±3

Estimated energy expenditure (actimeter)

B	Energy (kcal)	Energy(kcal)
08:15-12:15	504±59	491±51
12:15-20:15	970±288	1,068±263**
20:15-00:15	430±100	431±104
00:15-08:15	691±63	642±56*
Total	2,544±389	2,593±357

Values are mean ± SD. Paired *t*-tests indicate significant differences (n=12; *P*<0.05 and **P*<0.01) between the two sessions.

normal sleep (normal sleep: intake = 4,100±290 kcal; sleep restriction: intake=4,000±260 kcal). In the second study, Nedelcheva *et al.* (2009) studied eleven obese subjects (BMI=26.5±1.5 kg/m^2) for two periods of 14 days with nights lasting either 5½ or 8½ hr. At the end of each period, spontaneous food intake, plasma leptin and ghrelin levels and energy expenditure (by doubly labeled water) were measured. No significant variations were observed between the two situations for these parameters although snacking was higher after sleep deprivation (*P*<0.05). Analysis of these results revealed that here also subjects were in a positive energy balance in both situations, even in the situation of normal sleep (normal sleep: energy intake = 3,400±970 kcal, expenditure=2,400±370 kcal; sleep restriction: intake=3,700±900 kcal, expenditure=2,500 ±540 kcal). In the above two studies, in which food intake was very high compared with energy expenditure regardless of the duration of the sleep, subjects were placed in artificial experimental conditions: they were alone in a room with constant access to easily available palatable food (refrigerator or food distributor) and with low physical activity. Consequently, the effect of sleep duration was completely 'erased' by an excessive energy intake (≥4,000 kcal at rest). Moreover, and anecdotally, Schmid *et al.*'s team indicated this bias in an article published in 2011 'A potentially biasing influence of laboratory overeating has been previously observed', referring to the article cited above, and Nedelcheva *et al.* reported the complement of their results in a study entitled *Exposure to recurrent sleep restriction in the setting of high caloric intake and physical inactivity results in increased insulin resistance and reduced glucose tolerance.*

In contrast, our results are consistent with those of two others studies: Bosy-Westphall *et al.* (2008) noted, after four days of sleep restriction (one night of 7 hrs, two nights of 6 hrs then a night of 4 hrs), an increase in energy intake (2,500±500 kcal after the 7-4 hrs sleeps vs. 2,100 ± 250 kcal after normal sleep duration, P <0.05) and in bodyweight (+ 400 g, P <0.05) in 14 women (some were of normal weight, others overweight or obese). More recently, St-Onge *et al.* (2011) also observed an increase in energy intake after sleep deprivation: 30 normal-weight subjects had five nights of 4 hr sleep and five nights of 9 hr sleep. At the end of each period, food intake was measured and energy expenditure was evaluated (by doubly labeled water). The subjects consumed more, especially more fat, after sleep deprivation (2,800±600 kcal after 4 hr sleep vs. 2,500±600 kcal after the 9 hr sleep). In addition to these studies, it was recently reported that total sleep deprivation did not affect food intake in a calorie-rich buffet in the late afternoon under laboratory conditions (Benedict *et al.,* 2011) but was associated with increased preference for fatty food, snacking and eating in a restaurant (Nishiura *et al.,* 2010; Weiss *et al.,* 2010).

6.4 Synthesis of observations

Despite the two studies with conflicting results (Nedeltcheva *et al.,* 2009; Schmid *et al.,* 2009), there is agreement between epidemiological studies (see above), experimental observations in humans (hunger: Benedict *et al.,* 2011; Brondel *et al.,* 2010; Schmid *et al.,* 2008; Spiegel *et al.,* 2004, snacking or food intake: Bosy-Westphal *et al.,* 2008; Brondel *et al.,* 2010; Nedeltcheva *et al.,* 2009; Nishiura *et al.,* 2010; St-Onge *et al.,* 2011, hormonal changes: Mullington *et al.,* 2003; Omisade *et al.,* 2010; Pejovic *et al.,* 2010; Schmid *et al.,* 2008; Spiegel *et al.,* 2004) and in animals.

The vast majority of these studies suggest a direct link between acute or chronic sleep deprivation and increased food intake or obesity. Furthermore, it appears that sleep deprivation increases the consumption of energy-rich foods (Williams *et al.,* 2007), especially fatty foods (Brondel *et al.,* 2010; Schmid *et al.,* 2009; St-Onge *et al.,* 2011; Weiss *et al.,* 2010).

In practice, those who have already experienced sleep deprivation may have noticed they need more food to stay awake or crave high-energy foods or snacks during the following day. Another example, in trans-meridian flights where sleep is disrupted, the airlines served several in-flight meals and few people refused any of them. More worrying, dieticians and nutritionists often relate the problem they have with their patients when these patients have gained weight after the introduction of night work with reduced sleep.

6.5 Hypotheses about the mechanisms involved

The mechanisms underlying the deleterious effects of sleep deprivation on food intake are not well understood. The master clock mainly regulated by the suprachiasmatic nucleus of the hypothalamus clearly seems to play a role. This nucleus, present in all vertebrates, is involved in the circadian rhythms observed in the circadian organization of physiological functions (body temperature, sleep/wake rhythm, food intake, reproduction...). The functioning of the suprachiasmatic clock and its timing are essentially related to light (the clock is essentially reset by the light/dark cycle), but other factors such as nonphotic stimuli are involved in its operation either directly or indirectly through peripheral oscillators, such as the liver oscillator. Food intake, as well as food deprivation, is able to shift the master clock and/or modulate photic synchronization (Challet, 2007; Shibata *et al.,* 2010). The suprachiasmatic nucleus modulates food intake by its projections to many brain structures that control food intake (arcuate nucleus, paraventricular nucleus, lateral and dorsomedial hypothalamic areas). In addition, orexigenic neurons (neuropeptide Y/agouti-related protein) and anorexigenic neurons (proopiomelanocortin/cocaine- and amphetamine-regulated transcript) connect the arcuate nucleus to the suprachiasmatic nucleus (e.g. Yi *et al.,* 2006).

The master clock controls both food intake and the sleep/wake cycle, but nutritional factors and the sleep/wake cycle also provide feedback to the clock (e.g. Laposky *et al.,* 2008). Consequently, food intake has an impact on the sleep/wake cycle and the sleep/wake cycle has an impact on food intake. Actually, animal studies have shown that diet affects sleep or the sleep/wake cycle: starvation induces a reduction in sleep time (e.g. Danguir and Nicolaidis, 1979); a low calorie intake in rats during the day can alter the timing of the suprachiasmatic nucleus by light (e.g. Stephan, 2002); a high calorie fat diet is likely to advance food intake in the sleep/wake cycle. Conversely, as indicated previously, rats' sleep duration influences food intake since sleep deprivation induces almost constant hyperphagia.

Very interestingly, neurons found in the lateral and posterior hypothalamus in animals in 1998 affect both, the sleep/wake cycle and food intake: they are involved in the control of vigilance (which they stimulate e.g. Sakurai, 2007), appetite (they increase food intake e.g. Haynes *et*

al., 2002) and motor activity (which they increase e.g. Saper, 2006). These neurons have many projections in the brain and secrete orexin A and B (or hypocretin 1 and 2). These neurons receive direct afferents from the suprachiasmatic nuclei. Furthermore they are activated by sleep deprivation, hypoglycaemia and ghrelin, and they are inhibited by leptin (e.g. Sakurai, 2005). Therefore, the neurons secreting orexins A and B could play an important role in energy homeostasis (Huang *et al.,* 2011; Kalsbeek *et al.,* 2011; Laposky *et al.,* 2008; Nicolaidis, 2006; Penev, 2007): the animal is sleeping and not eating or it is active and not likely to eat.

6.6 Teleonomy: seasonal rhythm of food intake and sleep in animals?

The farther away from the equator, the greater the modifications in the day/night cycle with the changes in the seasons: at the poles, the days are long in summer while the nights are longer in winter. In summer, when periods of light predominate, animals must be vigilant (sleeping less), active and above all feed to build up reserves (Figure 6.4). Thus there is a natural programmed decrease in sleep and an increase in food intake. On the contrary, in winter, the animals sleep more and their activity must be reduced to save energy stores as food becomes scarce. In this case, sleep duration increases and food intake decreases. This seasonal variation in sleep and food intake according to the length of day and night is well known in many animal species
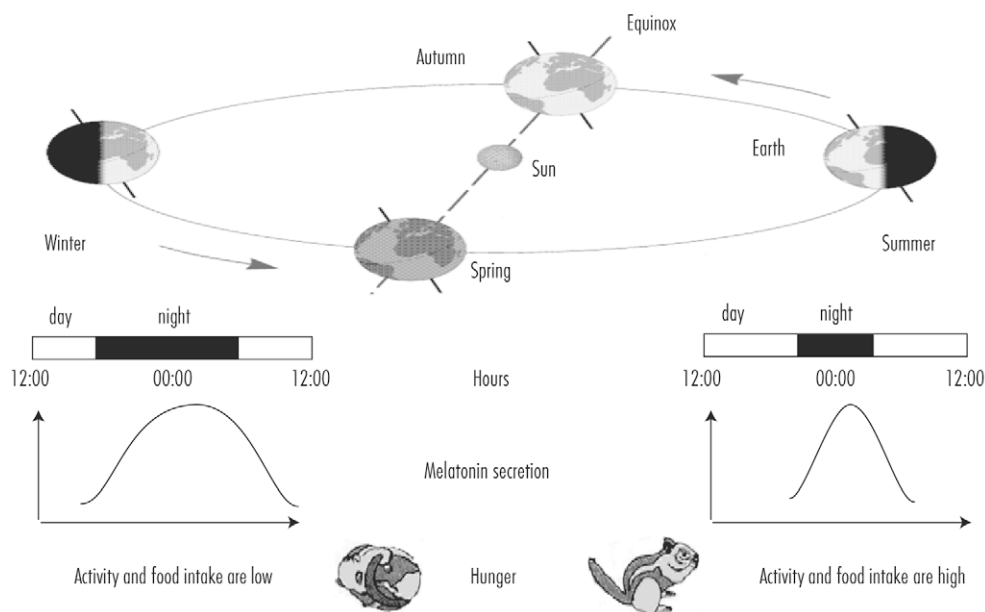
Figure 6.4. Seasonal rhythm of food intake and sleep in animals in the north hemisphere. In winter the nights are long and melatonin secretion is high. Then activity and food intake drastically decrease. In summer, the opposite effects are observed.

(marmot, raccoon dog, squirrel, hamster, bats, penguins...). Our hypothesis is that these archaic phylogenetic mechanisms are still present and active in humans. Several studies have shown that in temperate countries, sleep duration increases and food intake decreases in autumn compared to winter (De Castro, 1991; Ma *et al.*, 2006). This phenomenon could be mediated by melatonin secretion which varies seasonally. This hormone, closely associated with the suprachiasmatic nucleus, is involved in the sleep/wake cycle, food intake, motor behavior, reproduction, growth, animal's camouflage. Melatonin is used in the treatment of circadian disorders for people suffering from the effects of jet lag, shift work and winter depression. In each of these disorders, there are simultaneous changes in sleep and eating behavior or weight (e.g. Lewy *et al.*, 2006). Finally, genetic mutations of the internal clock (CLOCK genes) are frequently found in human obesity and could partially explain the ineffectiveness of weight loss treatment (Garaulet *et al.*, 2010). To add elements to this hypothesis, it seems that teams working during summer in stations located in Antarctica (24/24 light, lighting of more than 100,000 lux due to snow reflection) have great difficulty not to put on weight despite higher daily energy expenditure (Panin, 2007).

To our knowledge, the possible involvement of melatonin in sleep deprivation and its role in increasing food intake has not been tested. Thus we suggest assessing the eventual changes in food intake and/or in food preferences (particularly for fatty foods) after the implementation of a treatment with melatonin. These parameters could also be evaluated in relation to the possession of genes conferring some ability to resist sleep deprivation.

6.7 Conclusion

Sleep deprivation seems to be an incontestable risk factor for overweight and obesity, although the mechanisms are not yet fully understood. In prevention programs against overweight, in addition to recommendations on diet and physical activity, recommendations on sleep duration should therefore be included, especially if subjects reduce their sleep time for activities with little energy expenditure like watching television (one study found an association between a simultaneous decrease in sleep duration and an increase in BMI and in time spent watching television, Wells *et al.,* 2008). Of course, intervention studies are needed to draw conclusions about the beneficial role of sleep in the treatment of overweight or obesity. However, a study found that insufficient sleep decreases the effort to lose weight (after a low-calorie diet for 14 days, subjects lost 55% less fat and 60% more muscle when they slept 5½ hrs, compared with the period when they had nights of 8½ hrs, Nedeltcheva *et al.,* 2010). In the same way, another study has observed that short sleepers that increase their sleep time will gain less weight in six years (BMI: -1.1±0.36 kg/m2; body fat: -2.4±0.64 kg) than short sleepers who retain a reduced sleep time (Chaput *et al.,* 2010).

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Summary points

- Night eating syndrome (NES) is defined by the consumption of a significant proportion of total calorie intake after the evening meal, and/or nocturnal awakenings with food ingestion at least twice weekly. In addition, subjects' awareness of the eating episode is required, as a cause of distress or impaired functioning.
- The clinical features of NES are evening hyperphagia, nocturnal eating with insomnia and morning anorexia, i.e. a disruption of the circadian eating/sleeping pattern.
- Diagnostic criteria are provisional and there is an urgent need of validated criteria for comparison between different studies and for defining NES in the spectrum of eating disorders.
- The prevalence of NES is larger in obesity compared to non-obese population, but its role in obesity development is not proven.
- Retrospective reports suggest that NES follows a chronic course, exacerbated by stressful life situations.
- There is no satisfactory treatment of NES. Research is needed to develop more effective treatments of both NES symptoms and NES-associated obesity.

7. Night eating syndrome in obesity

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Abstract

Night eating syndrome is an eating disorder characterized by a delay in the circadian timing of food intake, which is remarkably reduced during the first part of the day and greatly increased after dinner, frequently with awakenings characterized by nocturnal food ingestion and morning anorexia. In the absence of standard diagnostic criteria, its prevalence is difficult to estimate. According to the most agreed criteria, the disorder affects approximately 1.5% of the general population, it is more common among obese persons and the prevalence increases with increasing adiposity. Longitudinal studies with adequate follow-up are needed to determine whether night eating contributes to weight gain and the development of obesity. The research should also aim to assess the interaction of genetic and environmental processes in the pathogenesis and in the maintenance of the disorder. There is no satisfactory treatment of night eating. Limited information is available on drug treatment (sertraline, topiramate). Lifestyle modifications aimed at weight loss are standard treatment whenever night eating is associated with obesity and have demonstrated a favorable effect, but more research is needed also in this area to optimize the protocols.

Keywords: diet, food intake, behavior therapy, night eating

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Abbreviations

BED	Binge eating disorder
BMI	Body mass index
CBT	Cognitive-behavioral treatment
NES	Night eating syndrome
NEQ	Night eating questionnaire
NESHI	Night eating syndrome history and inventory
SRED	Sleep-related eating disorder

7.1 Introduction

Night eating syndrome was first described by Stunkard *et al.* in 1955 as a stress-related eating disorder consisting of morning anorexia, evening hyperphagia and insomnia, with awakenings characterized by nocturnal food ingestion. The condition had been ignored for several decades and only recently NES has become the focus of intense scientific investigation. The main clinical aspect is a delay in the circadian timing of food intake, which is remarkably reduced during the first part of the day and greatly increased in the second part.

7.2 Definition and diagnostic criteria of night eating syndrome

In 2010, the International NES Working Group proposed provisional diagnostic criteria for NES research (Table 7.1) (Allison *et al.*, 2010b). The core criterion is an abnormally increased food intake in the evening and nighttime, manifested by: (a) consumption of at least 25% of calorie intake after the evening meal; and/or (b) nocturnal awakenings with food ingestion at least twice a week. In addition, the diagnosis also requires subjects' awareness of the eating episode, as a cause of distress or impaired functioning. The clinical picture should also be characterized by at least three of the following five clinical features: (a) morning anorexia and/or omitted breakfast four mornings per week or more; (b) strong urge to eat between dinner and sleep onset and/or during the night; (c) difficulties in sleep onset and/or sleep maintenance four nights per week or more; (d) personal belief that one must eat in order to initiate or return to sleep; (e) frequently depressed mood and/or mood worsening in the evening. These criteria must be met for 3 months or more.

At present, NES is included in the Feeding and Eating Conditions Not Elsewhere Classified by the working group of the forthcoming Diagnostic and Statistical Manual of Mental Disorders (DSM-V; see http://www.dsm5.org), since insufficient data are so far available to justify this condition being designated as 'disorder'.

Table 7.1. Historical evolution of the Night Eating Questionnaire (NEQ). The different versions are listed in chronological order, with the specific behavioral/psychological contents considered by the various items.

NEQ versions	No. of items & scoring system	Questions considered in the assessment
Original unpublished version	9 items: 4-point scale	Morning anorexia (2 items) Evening hyperphagia (1 item) Initial insomnia (1 item) Mid-phase insomnia (1 item) Nocturnal ingestion (1 item) Mood (3 items)
Revision, 2004 (Marshall *et al.*, 2004)	9+6 items: 5-point scale	Morning hunger and timing of first food consumption (2 items) Percentage of calories consumed after supper Trouble sleeping Frequency of nocturnal awakenings and ingestion of food (2 items) Level of awareness Level of feeling blue Mood lower Cravings to eat after supper Cravings to eat when awake Need to eat to fall back to sleep Control over night eating Duration with NES (years)
Revision, 2008 (Allison *et al.*, 2008b)	14 items: 5-point scale	Morning hunger and timing of first food consumption (2 items) Percentage of food consumed after dinner (1 item) Initial insomnia (1 item) Mood disturbance (2 items) Food cravings and control over eating behavior both before bedtime (2 items) and during night time awakenings (2 items) Frequency of nocturnal awakenings and ingestion of food (3 items) Awareness of nocturnal eating episodes (1 item)

7.3 Distribution of night eating syndrome in obesity

The overall prevalence of NES has been estimated at 1.5% (Rand *et al.*, 1997), a prevalence similar to BED and higher than those of anorexia and bulimia nervosa. Although NES also occurs among non-obese persons, it is more common among obese persons and its prevalence increases with increasing adiposity. An early study in an obesity clinic reported a prevalence of NES of 8.9% (Stunkard *et al.*, 1996). More recently, in a Swedish population based study (Tholin *et al.*, 2009), the prevalence of NES was 2.5 times more common among obese males and 2.8 times more common among obese females than among normal-weight men and women. A strong relationship exists between overweight status and NES and in obese patients entering a weight loss program NES prevalence ranges from 6% (Ceru-Bjork *et al.*, 2001) to 14% (Gluck *et al.*, 2001). Also in a psychiatric population, NES prevalence increases with BMI (Lundgren *et al.*, 2006a).

The prevalence of NES among bariatric surgery candidates is controversial. One survey of patients undergoing surgery for morbid obesity reported a high prevalence of NES (27%) (Rand *et al.*, 1997) and similar data were reported in a large Australian sample (Colles *et al.*, 2007) and in an old American study carried out by an eating disorder unit in subjects undergoing vertical banded gastroplasty (42% (Hsu *et al.*, 1996)). In contrast, in a recent study where the diagnosis for NES was based on graded diagnostic criteria, only 1.9% of participants met the diagnostic criteria for NES at interview for the strictest definition and 8.9% across all definitions of NES. Self-reported prevalence of NES was much higher (Allison *et al.*, 2006). According to a 2003 review (De Zwaan *et al.*, 2003), NES prevalence among groups of obese persons seeking surgical weight loss can range from 6% to 64%.

It is not yet clear whether NES precedes and contributes to the development of obesity. A study on consecutive participants with class II–III obesity found no differences between the 27 participants (10.1%) with NES and the 239 (89.9%) participants without NES in BMI, BMI at age 20, maximum BMI and previous weight loss attempts. These data indicate that night eating has a marginal role in the severity and in the history of obesity (Calugi *et al.*, 2009). On the contrary, a few studies suggested that night eating could be a pathway to obesity. Marshall *et al.* (Marshall *et al.*, 2004) reported that normal-weight night eaters were younger (33.1±10.7 years) than obese night eaters (43.1±9.6 years, *P*<0.01). Furthermore, night eaters reported that they were of normal weight prior to the development of NES, which heralded weight gain. Spaggiari *et al.* (1994) confirmed that night eating preceded the onset of obesity in most cases. Further research is however needed to conclude whether NES contributes to obesity or obesity promotes NES.

7.4 Assessment of night eating syndrome

NES can be assessed both by self-reported questionnaire and by direct interview. The NEQ is a self-reported screening instrument based on several items related to food intake in relation to sleep and day-time events. The first unpublished version, dating back to 1955, included a 9-item

measure with a 4-point Likert scale. It considered morning anorexia, evening hyperphagia, initial and mid phase insomnia, nocturnal food ingestion and mood. Later, 6 more items were included and the questionnaire was converted into a 5-point scale (Marshall *et al.*, 2004). The new items regarded the levels of morning hunger and the percentage of calorie intake consumed after dinner. In 2008, Allison *et al.* (2008b) excluded one question to diminish the contribution of mood to the final score (Table 7.1). Unfortunately, there is no general agreement about the cut-off score for diagnostic purposes; a cut-off score of 25 was suggested as appropriate for screening purposes, but a value of 30 might be better to reduce false positives (Allison *et al.*, 2008b).

The NESHI is an unpublished semi-structured interview designed to confirm the diagnosis of NES. It assesses the typical 24-hr food intake with a recall of all meals and snacks, the sleeping pattern, mood and life stressors, weight and diet history, and previous treatment strategies for NES. On the basis of all meals and snacks recall, the interviewer may estimate the exact caloric intake after the evening meal and how often nocturnal food intake occurred in the previous 3 months. The NESHI can be used with minimal adaptation to assess the presence of the diagnostic criteria of NES.

7.5 Pathogenesis of night eating syndrome

The cause of NES is not known and several questions about its pathogenesis have not yet been clarified. In the absence of solid data, it is definitely premature to present a unifying causal model and therefore we shall report in the following paragraphs only the main available empirical data.

7.5.1 Genetics

A study of 5- to 6-year old children reported that offspring of mothers with night eating behavior were more likely to become night eaters compared to children of non-night-eating mothers (Lamerz *et al.*, 2005). Another study comparing night eating in NES families to control probands found that the odds of a patient with NES (diagnosed by NEQ) of having an affected first-degree relative were much greater than those of controls (OR=4.9) (Lundgren *et al.*, 2006b). Finally, in adult twins the genetic association between night and binge eating was around 0.60, suggesting the presence of common genetic factors influencing the development of both eating behaviors (Root *et al.*, 2010).

7.5.2 Neurobiological findings

Some studies found that people with NES have higher levels of adrenocorticotropic hormone and cortisol throughout the day. However, the production of cortisol in NES showed a normal circadian pattern (higher levels in the early morning falling during the course of the day) (Birketvedt *et al.*, 1999), indicating that the hormonal pattern, however high, was not shifted, contrary to the eating pattern (Allison *et al.*, 2004). Night eaters are also characterized by a reduced adrenocorticotropic hormone and cortisol response to corticotropin-releasing hormone.

This response might be the expression of secondary failure of the hypothalamic-pituitary-adrenal axis (Birketvedt *et al.*, 2002), a pattern associated with stress which also triggers overeating (Epel *et al.*, 2000).

In 2005, Allison *et al.* found that ghrelin levels were lower in patients with NES than in controls from 01:00 hr to 09:00 hr; in addition, insulin was higher at night and lower in the morning, and glucose was non-statistically higher at night in patients with NES than in controls. The circadian profiles of thyroid-stimulating hormone, cortisol, melatonin, leptin and prolactin did not differ between groups. However, delays of 1.0-2.8 hrs were found in leptin and insulin acrophase and in the circadian rhythm of melatonin (with a trend for a delay in the circadian cortisol rhythm) of NES patients (Goel *et al.*, 2009). In contrast, circulating levels of ghrelin were phase advanced by 5.2 hrs. The glucose rhythm showed an inverted circadian pattern. Patients with NES also showed reduced amplitudes in the circadian rhythms of food intake, cortisol, ghrelin and insulin, but an increased amplitude in the rhythm of thyroid-stimulating hormone.

Melatonin appears to induce and maintain sleep (Zhdanova *et al.*, 1996). Diminished melatonin levels have been associated with impaired sleep (Haimov *et al.*, 1995) and a low nocturnal rise in melatonin may play a role in the nighttime awakenings of NES patients.

Finally, food selection mainly involves carbohydrates during night-eating episodes. As carbohydrates increase tryptophan availability and transport into the brain and conversion to serotonin resulting in facilitation of sleep, night eating might be a teleological response to restore the disrupted sleep. No data are available on the neurobiological pattern before NES onset or after NES recovery to determine whether neuroendocrine changes observed in NES are cause or effect of the disorder.

7.5.3 Psychological and behavioral processes

No satisfying psychological theory has been proposed to account for the development and maintenance of NES. Stunkard *et al.* (1955), in his original report, noted that night eating worsened with stress and was alleviated by removing the person from the stressful environment. Subsequent studies found that life stress and/or depression were often associated with the onset of night eating and seemed to play a key role in its maintenance. A few consequences of night eating (e.g. gaining weight, worsening of body image, tiredness and health problems) might indeed maintain stress and depression (Allison *et al.*, 2004).

Recently, the central role of cognitions and emotions has been emphasized in the maintenance of disorder. In particular, nocturnal eating episodes might be maintained by the belief that one must eat in order to fall asleep (Vinai *et al.*, 2008) and by the anxiety of not being able to sleep without eating (Sassaroli *et al.*, 2009).

Four main NES categories have been identified (Allison *et al.*, 2004), having specific dysfunctional thoughts maintaining the disorder: (a) *the compelled evening and nighttime overeater* (e.g. 'The cake that I ate an hour ago was good, I absolutely must eat another slice, I need it'); (b) *the anxious/agitated night eater* ('I am too anxious; I cannot sleep; I have to eat something to calm myself'); (c) *the craving night eater* ('I am tired, but I wish to eat something sweet, so I'll go and get it now'); and (d) *the all-or-nothing belief about sleep and night eater* (I am very tired, if I do not eat I shall not fall asleep; if I eat I'll sleep').

People with NES have distinctive eating pattern characterized by small or no intake of food at breakfast and two moderate small sized meals at midday and early evening. This pattern of eating might trigger an intense hunger in the late evening and/or produce sleeping problems, two conditions that may facilitate the development of evening hyperphagia and nocturnal eating episodes. Finally, some food-associated environmental stimuli (e.g. presence of food at home that stimulates eating, such as ice cream, cookies, easily accessible places where food is stored), sleep-hindering stimuli (e.g. taking caffeine or other substances affecting sleeping, working with the computer in the evening, going to bed when not sleepy, giving too much importance to sleep and worrying about the negative consequences of non sleeping) might also contribute to the maintenance of both night eating and sleep problems.

Figure 7.1 shows a schematic representation of the principal factors implicated in the maintenance of NES.
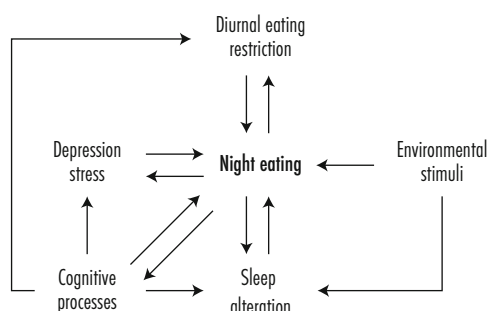
Figure 7.1. Schematic representation of the principal mechanisms implicated in the maintenance of the night eating syndrome. Night eating is probably maintained by a complex interaction of several mechanisms including diurnal eating restriction (e.g. no intake of food at breakfast and small-sized meals at lunch and early evening), sleep alterations (e.g. difficulty falling asleep and nocturnal awakenings), depressive state and stress, environmental stimuli (e.g. the presence of food at home that stimulates eating) and cognitive processes (e.g. thinking of not being able to fall back to sleep without eating), all interacting with each other.

7.6 General clinical features

7.6.1 Evening hyperphagia and nocturnal eating

The definition of evening hyperphagia requires the assessment of two features: (1) the timing of food intake ('evening') and (2) the proportion of caloric intake ('hyperphagia'). The NES Working Group (Allison *et al.*, 2010b) defined evening hyperphagia as 'at least 25% of food intake is consumed after the evening meal'. The rationale of this threshold derives from the several observations. First, the criterion '25% of food intake' comes from one-week food journals completed by NES and control participants (O'Reardon *et al.*, 2004a). NES participants consumed 35% of their daily caloric intake after the evening meal with a standard deviation of 10%, in comparison with the 10% (standard deviation 7%) of non-NES. Second, the criterion 'after the evening meal' was chosen because the timing of evening meal may vary across countries, according to cultural habits.

Nocturnal eating is the other key-point among the clinical feature of NES. In comparison with people suffering from SRED, who eat in a sleep-walking state, who consume non-food or strange food (e.g. cigarettes or pet food) and have partial or complete amnesia for what they eat, individual with NES are usually aware of their eating behavior and recall their food intake the following day.

7.6.2 Morning anorexia

Morning anorexia leading to skipping breakfast, initially described as a core clinical feature of NES, is no longer considered essential for the diagnostic purposes (Allison *et al.*, 2010b; Striegel-Moore *et al.*, 2009). Hunger ratings were indeed at the highest during nocturnal eating episodes, but might be high also in the morning in subjects with night eating (Boseck *et al.*, 2007). The score of the NEQ item measuring morning anorexia did not correlate with the NEQ total score or the NEQ Evening Hyperphagia subscale and correlated only modestly (r=0.25) with the NEQ Nocturnal Eating subscale, as also confirmed in a reanalysis of 1,481 participants of six separate studies (Allison *et al.*, 2008a).

7.6.3 Insomnia

Two main sleep difficulties have been described in individuals with NES: difficulty falling asleep (≈50% of times) and nocturnal awakenings for reasons other than going to the toilet (more than once a week) (Striegel-Moore *et al.*, 2009). The results of the item response theory analysis of NEQ showed that these two behaviors discriminate between 507 individuals with and 972 individuals without evening hyperphagia or nocturnal eating (Allison *et al.*, 2008a).

7.6.4 Clinical depression

The presence of depressed mood has been described in several clinical samples (Birketvedt *et al.*, 1999; De Zwaan *et al.*, 2006; Gluck *et al.*, 2001) and may be considered specific of NES. In an

observational case-control study in obese patients, depression was the only variable associated with NES, the association was not influenced by binge eating, and almost half of NES cases reported severe depressive symptoms (Calugi *et al.*, 2009). Depressed mood might be related to the lack of control and sense of helplessness that NES individuals experience over their night eating and was also associated with a feeling of guilt and shame (Allison *et al.*, 2010b).

Finally, NES individuals may show a worsening of mood in the course of the day (Striegel-Moore *et al.*, 2006), a pattern opposite to that of melancholic depression, but this pattern was not universally observed (Allison *et al.*, 2010b).

7.6.5 Eating disorders

About 7-25% of individuals with NES also meet the DSM-IV proposed criteria for BED (Allison *et al.*, 2007, 2005b; Greeno *et al.*, 1995; Stunkard *et al.*, 1996; Tzischinsky and Latzer, 2004). NES and BED share evening hyperphagia (Allison *et al.*, 2010b); however, two main features distinguish NES and BED. First, the nocturnal eating episodes of NES were associated with the belief that eating is mandatory to fall asleep (Vinai *et al.*, 2008) and with anxiety, whereas the nocturnal eating episodes of BED had no correlation with this belief and with emotions (Sassaroli *et al.*, 2009). Second, the evening and nocturnal eating episodes of NES individuals did not involve much food (about 300 kcal) (Birketvedt *et al.*, 1999), while they were much larger in BED episodes.

The prevalence of NES among individuals with bulimia nervosa is about 9% (Tzischinsky and Latzer, 2004), whereas NES has never been reported in anorexia nervosa.

7.6.6 Medical complications

The relationship between NES and the medical complications of obesity has been scarcely evaluated. A NES prevalence of 9.7% has been reported in diabetes and participants with night eating symptoms were more likely to be obese, to have unsatisfactory metabolic control and two or more diabetes complications (Morse *et al.*, 2006). In obese persons with type-2 diabetes, NES was more frequent than BED (3.8 vs. 1.4%) (Allison *et al.*, 2007). An observational case-control study found no significant differences in the prevalence of the metabolic syndrome between obese patients with and without NES (Dalle Grave *et al.*, 2011).

7.7 Management of obesity-associated night eating syndrome

No prospective studies on the natural course of NES in community samples have been published. Prognostic information only derives from retrospective reports, suggesting that the disease follows a chronic course, exacerbated by stressful life situations.

Since the early report of psychodynamic therapy focusing on stress reduction (Stunkard, 1976), the treatment of NES has been carried out using drugs, cognitive behaviour therapy, weight loss lifestyle modification and bariatric surgery.

7.7.1 Drug treatment

Limited information is available on the pharmacological treatment of NES. An open-label, unblinded study of 12-week sertraline treatment found that completers reduced caloric intake at night and the number of nocturnal awakenings and NES episodes (O'Reardon *et al.*, 2004b). A study *via* tele-medicine with sertraline found a reduction of evening hyperphagia and a decrease of 3 kg in overweight and obese participants (Stunkard *et al.*, 2006). Finally, in a double-blinded, placebo controlled randomized study, 71% of the participants allocated to the sertraline group (50-200 mg/day) were classified as responders compared to 18% in the placebo group (O'Reardon *et al.*, 2006). Overweight and obese participants in the sertraline group lost significantly more weight (-2.9 kg vs. -0.3 kg in the placebo). NES symptoms were improved by the second week of treatment, indicating an early effect of sertraline.

Another potentially useful drug is topiramate, an anti-seizure agent with anorexic effects, that had a positive effect in three of four treatment-resistant patients (two with NES and two with SRED), with a mean weight loss of 11.1 kg (Winkelman, 2003). Sedating agents are not effective and may exacerbate night eating (Howell *et al.*, 2009). In particular zolpidem should be avoided, as it is associated with unconscious nocturnal eating.

7.7.2 Cognitive-behavioral treatment

The rationale for CBT use in NES treatment came from the observation that this form of psychotherapy is effective in addressing eating, sleeping, mood and stress disorders (Morin, 2006), a combination of features commonly observed in NES.

The manual-based treatment for NES consists of ten individual one-hour sessions (once a week for the first eight weeks and once every two weeks for the last two sessions), and is divided into three stages (Allison *et al.*, 2010a):
- Stage 1 (sessions 1-4): focus on developing therapeutic alliance; explaining the rationale for CBT; educating participants on monitoring the disturbances in sleeping, eating, mood, and the automatic thoughts associated with night eating (e.g. 'I won't be able to fall back to sleep if I don't eat') and on teaching behavioural techniques and their modifications.
- Stage 2 (sessions 5-8): focus on strengthening coping skills developed in the first phase and challenging automatic thoughts. This stage also addresses how to improve sleep hygiene (e.g. no food in the bed room, no sleeping with television, set standard bedtime and morning awakening times), how to manage stress using breathing control and progressive muscle relaxation and how to implement physical exercise.

- Stage 3 (sessions 9 and 10): review of the progress and successes and focus on increasing self-efficacy, generating ideas regarding how to anticipate future problems and on relapse prevention.

The authors consider weight status as an important feature in treatment selection. In particular, normal weight patients with NES develop high rates of weight and shape concerns when they are educated to shift their caloric intake to day-time. For these patients weighing during sessions reduces worries about weight gain: if night eating is reduced and daytime food intake is increased, the weight remains stable or even decreases.

A pilot study of this specific CBT applied to NES patients showed that treatment reduced caloric intake after dinner (35.0% to 24.9%), the number of nocturnal episodes (8.7 to 2.6 per week), weight (82.5 to 79.4 kg) and the night eating symptom scale score (from 28.7 to 16.3; all P values <0.0001). The treatment was also associated with an improvement of depressed mood and quality of life (Allison *et al.*, 2010a).

7.7.3 Weight loss lifestyle modification

An observational case-control study measured weight loss outcome in obese individuals with NES (32 cases) and 68 non-NES matched participants entering a CBT weight-loss program (21-day inpatient treatment followed by a 6-month outpatient follow-up, described below) (Dalle Grave *et al.*, 2011). The time course of weight loss did not differ between groups throughout the study period (Figure 7.2); at 6-month follow-up, only 8 NES participants (22.8%) maintained a behavior compatible with the diagnosis of NES, and 51.4% of participants with NES at baseline did no longer report any night eating episodes in the previous 3 months. The larger BMI losses at 6-month follow-up were related to more severe binge eating and to lower body shape dissatisfaction, not to night eating. These data indicate that night eating does not hinder an obesity treatment based on lifestyle modifications with an initial inpatient phase. The mechanisms proposed to explain these results are the following:

- the initial phase of inpatient treatment facilitates the immediate abstinence from night eating because patients do not have access to food during the night;
- the pattern of "regular eating" with three main meals (i.e. breakfast, lunch and dinner) and one afternoon snack, imposed during hospital admission, by modifying the typical 'delayed eating' of individuals with NES (i.e. consuming most of the daily food during the last part of the day) possibly reduces craving for food during late evening and night;
- the adoption of cognitive behavioral strategies may increase the control over eating (e.g. self-monitoring, alternative behaviors to address hunger and eating triggers, problem solving and cognitive restructuring techniques to address weight loss obstacles);
- the involvement of significant others creates a positive home environment facilitating the patients' efforts to change.
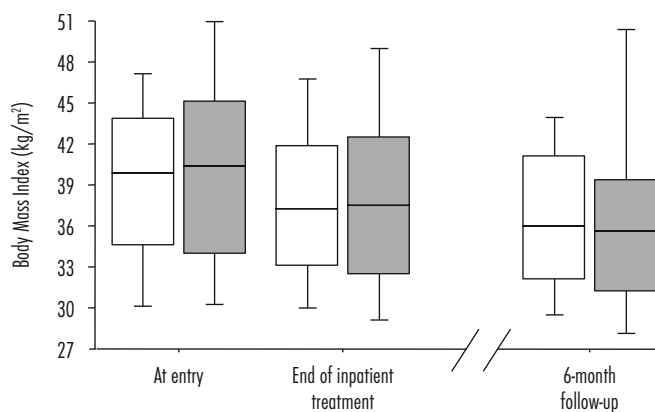
Figure 7.2. Box plots of body mass index at baseline, at the end of the inpatient program and at 6-month follow-up in obese individuals without night eating syndrome (NES) (white bars) and with NES (grey bars). In these 'box and whiskers' plots, the bar within each column represents the median value, the upper and lower borders of the box are the quartiles and the 'whiskers' (error bars) at the extremities indicate the 10th and the 90th percentiles. Note the progressive reduction of BMI from pre-treatment values to the end of the inpatient treatment ($P<0.001$) and to the end of follow-up ($P<0.001$ vs. baseline) in both groups. Whereas BMI at 6-month follow-up was reduced further in subjects without NES, compared with end of inpatient treatment ($P<0.001$), no additional BMI reduction was observed in NES cases ($P=0.124$) (Dalle Grave *et al.*, 2011).

Diet and physical activities are incorporated into a program based on psycho-educational groups, practical activities and groups with significant others to create a positive environment supporting patients when they return home.

Procedures of the 21-day inpatient CBT weight loss program applied to NES patients:
1. low calorie diet (1,200 kcal/day for women and 1,500 kcal/day for men; 55% energy from carbohydrates, 15% from proteins and 30% from fats);
2. 30 min per day of bicycle exercise and two 45-min sessions per week of calisthenics;
3. 15 psycho-educational group sessions on lifestyle modifications, including the following topics:
   • self-monitoring (with practical exercise to calculate the daily energy intake and energy expenditure)
   • checking and interpreting body weight changes
   • weight goal setting (weight loss of 0.5 to 1 kg/week)
   • meal planning
   • strategies to improve stimulus control
   • alternative behaviors to address the factors triggering hunger and eating
   • problem solving
   • cognitive restructuring techniques to address the dysfunctional thoughts that hinder the
   • adherence to lifestyle modifications

4. practical activities designed to help patients reduce the speed of their eating pattern, make small portions of food, leave some food in the plate, stick to the diet when in restaurants and tolerate hunger after skipping a meal;
5. two groups with significant others (i.e. those who have influence on the eating behavior of the patients) to discuss how to create a positive home environment to support patients' efforts to change.

7.7.4 Bariatric surgery

A study found no changes in the frequency of night eating three years after bilio-pancreatic diversion (Adami *et al.*, 1999); another study showed less stability in the diagnosis of NES one year after laparoscopic adjustable gastric banding (Colles *et al.*, 2008). The diagnosis of NES was not associated with weight loss, night eating post-surgery or other measures of eating pathology.

Conflicting findings were also reported by retrospective studies. A self-reported form completed by 111 patients three year after gastric restriction surgery showed that 57.6% fulfilled NES criteria before surgery and 27% post-surgery (Rand *et al.*, 1997). Another study found an impressive change in the prevalence of nocturnal eating tested by the Eating Disorder Examination Interview (Grilo and Masheb, 2004) (from 55% to 2% after surgery).

7.8 Clinical and research priorities

Several clinical and research priorities emerge from this review. First, we need to have a general consensus on the definition of NES. The NES working group provisional diagnostic criteria provide the opportunity to collect data on the prevalence and clinical significance of each of the proposed criteria and on the possible clustering of the symptoms into a syndrome (Striegel-Moore *et al.*, 2009). These studies might also help to determine whether NES is distinct from other eating disorders, if a diagnosis of NES is of any clinical utility to be classified as a distinctive eating disorder. Second, long-term follow-up studies are expected to assess whether NES contributes to weight gain and to the development of obesity. Third, studies should clarify if depression and stress are risk and/or maintaining factors of NES or are secondary to NES-associated obesity. Fourth, twin studies, as well as genome-wide linkage and association studies might throw light on NES pathogenesis. The search for genes associated with NES might benefit from studies of associated phenotypes, such as obesity and BED. The research should also aim to assess the interaction of genetic and environmental processes and the psychological factors maintaining the disorder. Finally, there is an urgent need for more research of effective treatments both to address the symptoms of NES and to manage obesity often associated with this disorder.

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Summary points

- After food intake the gut signals increase sleepiness by modulating the central nervous sleep centers through absorbed nutrients, gastrointestinal neuro-humoral transmitters and autonomic nervous afferents.
- Patients with functional dyspepsia, i.e. complaining of chronic or recurrent epigastric pain or discomfort in absence of structural or biochemical alterations, may also refer to drowsiness after a normal everyday meal that interferes with daily activity.
- Differently from the usual, and immediately postprandial, dyspeptic symptoms, drowsiness occurs late after the meal.
- Compared to healthy subjects, functional dyspeptic patients have an increased after meal gastric antral distension.
- After meal drowsiness in functional dyspeptic patients is time related with antral volume variation since it follows the antral distension and lasts as long as the antrum remains distended.
- Functional dyspeptic patients referring to postprandial drowsiness have a greater probability of having delayed gastric emptying than healthy subjects and functional dyspeptic patients not referring to postprandial drowsiness.
- It appears that postprandial drowsiness can be induced by the antral distension and the delayed gastric emptying, that, prolonging the inflow of gastric contents into the duodenum, maintains a sustained release of neuroendocrine stimuli and activation of the vagal afferents affecting the central nervous sleep centers.

8. Postprandial drowsiness in dyspepsia

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Abstract

Functional dyspepsia (FD) is widely used in clinical practice to describe a symptom complex that always includes chronic or recurrent pain or discomfort in the upper abdomen in absence of structural or biochemical abnormality. Specific dyspepsia symptoms comprise epigastric pain, postprandial fullness, early satiation, and epigastric burning however, FD patients frequently reported other symptoms not referable to the gastrointestinal (GI) tract, including headache and drowsiness. Drowsiness is a common sensation often and variably reported also by healthy subjects. Bi-directional brain-gut interactions play an important role in the regulation of digestive process, including appetite and food intake, in health and disease. Feeding behavior is dependent upon the integration of metabolic, autonomic, endocrine, and environmental factors coordinated with an appropriate state of cortical arousal. The hypothalamus has been regarded to play a pivotal role in maintaining energy homeostasis. The arcuate nucleus modulates satiety in response to metabolic signals, neuropeptides released postprandially by the GI tract, and vagus nerve stimulation. The arcuate nucleus integrates these signals and transmits them to the ventromedial hypothalamus, that indirectly, through the inhibition of lateral hypothalamic area, stimulates the sleep centres. It has been hypothesized that an alteration of brain-gut interactions may underlie the symptom generation in functional gastrointestinal disorders and may be involved in the pathophysiology of various eating disorders. An over distension of the gastric antrum has been found in a subgroup of patients with FD complaining of postprandial drowsiness. In these dyspeptic patients postprandial drowsiness occurs later than the usual gastrointestinal dyspeptic symptoms and is associated with antral distension and delayed gastric emptying. The onset of drowsiness is usually preceded by an increment of antral distension and the duration of the symptom appears to be related to the persistence of antral distension. Several substances, released and/or inhibited as result of antral distension and/or delayed gastric emptying might be involved in mediating postprandial drowsiness in FD patients.

Keywords: antral distension, functional dyspepsia, postprandial drowsiness

Abbreviations

5-HT	Serotonin
AgRP	Agouti-related peptide
ARC	Arcuate nucleus
CART	Cocaine and amphetamine regulated transcript
CCK	Cholecystokinin
CNS	Central nervous system
FD	Functional dyspepsia
FGID	Functional gastrointestinal disorders
FODMAP	Fermentable oligo-di, mono-saccharides and polyols
GI	Gastrointestinal
GLP-1	Glucose-like peptide
IBS	Irritable bowel syndrome
LHA	Lateral hypothalamic area
NPY	Neuropeptide Y
NTS	Nucleus tractus solitarius
POHA	Preoptic hypothalamic areas
POMC	Pro-opiomelanocortin
PYY	Peptide –YY
VIP	Vasoactive intestinal peptide
VMH	Ventromedial hypothalamus

8.1 Introduction

The term dyspepsia is widely used in clinical practice to describe a symptom complex that always includes chronic or recurrent pain or discomfort in the upper abdomen. Although dyspeptic symptoms may result from a number of organic causes such as peptic ulcer disease, pancreatico-biliary disease, and malignancy, the majority of patients with dyspepsia have no identifiable organic aetiology for their symptoms and, based on the Rome Diagnostic Criteria, are currently diagnosed as having functional dyspepsia (Tack *et al.,* 2006). Functional gastrointestinal disorders are disorders of the digestive system in which symptoms cannot be explained by the presence of structural or biochemical abnormality, therefore in absence of biomarkers FGID are diagnosed by clinical symptoms (Drossman, 2006). Specific dyspepsia symptoms comprise epigastric pain, postprandial fullness, early satiation, and epigastric burning however, most patients complain of multiple GI symptoms that are usually associated with food ingestion (Piessevaux *et al.,* 2003) and, overlap of symptoms with gastroesophageal reflux and other functional gastrointestinal disease is a frequent occurrence (Talley *et al.,* 1991). In addition to the usual dyspeptic symptoms FD patients frequently reported related to meal ingestion, as bothersome other symptoms not referable to the GI tract, including headache and drowsiness (Corinaldesi *et al.,* 1987; Distrutti *et al.,* 2002; Pallotta *et al.,* 2005; Talley *et al.,* 1991). Drowsiness is a common sensation (Orr *et al.,*

1997; Smith *et al.,* 1991; Stahl *et al.,* 1983; Wells *et al.,* 1997, 1998) often and variably reported by healthy subjects and may also influence the food intake (Parker *et al.,* 2004).

## 8.2 Interaction between metabolic signals and cortical arousal

In health bi-directional brain-gut interactions play an important role in the regulation of digestive processes (including appetite and food intake), in the modulation of the gut-associated immune system, and in the coordination of the overall physical and emotional state of the organism with activity in the GI tract (Mayer *et al.,* 2006).

Feeding behaviour is dependent upon the integration of metabolic, autonomic, endocrine, and environmental factors coordinated with an appropriate state of cortical arousal. The hypothalamus has been regarded to play a pivotal role in maintaining energy homeostasis by integrating these factors. Preoptic hypothalamic areas, especially the ventro-lateral preoptic nucleus and the median nucleus are the major sleep centers (Kim and Lee, 2009) while ventro-medial hypothalamus controls satiety and lateral hypothalamic area controls hunger. VMH and LHA together with the ARC interrelate in the control of energy status in response to blood energy signals. Several studies have related metabolic states to sleep, being LHA an important 'hunger center' and ARC being an important 'satiety center'. The ARC integrates metabolic signals through expression of NPY, AgRP, POMC, and CART. NPY and AgRP induce hunger by inhibiting the VMH and stimulating the LHA, POMC and CART promote satiety by activating VMH and inhibiting LHA (Kim and Lee, 2009) (Figure 8.1 and 8.2). Thus in response to metabolic signals ARC might induce hunger or satiety by alternatively inhibiting or stimulating the VMH and the LHA, respectively. LHA normally promotes also arousal and reduces sleepiness. Therefore in response to food signals the ARC, may indirectly induce drowsiness by inhibiting the LHA (Kim and Lee, 2009). This may explain why high energy meals produce more drowsiness than low energy ones and why VMH-damaged rats did not experience drowsiness during food repletion after deprivation compared to controls, (Danguir and Nicolaidis, 1979).

Several theories have been proposed concerning mechanisms of how food intake may affect cognition and wakefulness. Of these the belief that postprandial drowsiness is caused by redistribution of blood flow from cerebral to mesenteric vessels resulting in relative cerebral hypoxia is contradicted by a neurophysiologic principle that cerebral perfusion is maintained under a wide range of physiologic state and by recent evidence that there is no measurable change of blood flow in the common carotid artery during and after eating (Bazar *et al.*, 2004).

An alternative theory is that various macronutrients differently affect the rate of gastric emptying, the glycaemic index and the insulin response may modulate the state of alertness. In particular it has been shown that a rapid postprandial decrease in glycaemia level is associated to a better performance in decision time level in young adults (Lowden *et al.*, 2004). Another hypothesis is that the increase of L-tryptophan demand, and serotonin 5-HT synthesis induced after meal in the brain by the released insulin, induces drowsiness (Kim and Lee, 2009). This implies that
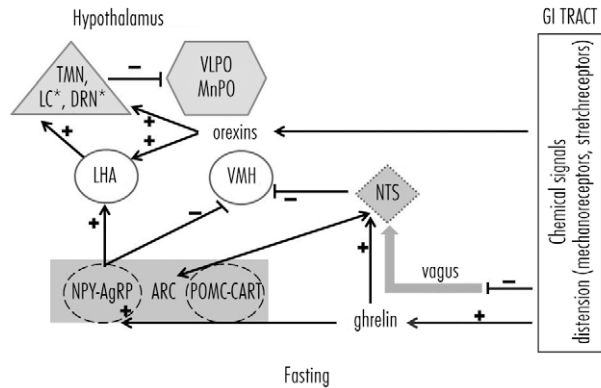
Figure 8.1. Afferent gastrointestinal signals controlling food intake and arousal: fasting condition. In fasting condition metabolic, neuro-hormonal signs release ghrelin and orexins. The increased level of ghrelin activates the arcuate nucleus (ARC) and nucleus tractur solitarius (NTS) that through the expression of neuropeptide Y (NPY) and agouti-related peptide (AgRP) activate the lateral hypothalamic area (LHA) and inhibit the ventro-medial hypothalamus (VMH). The LHA in turn activates the arousal centres. The increased level of orexins activates directly both LHA and arousal centres. *The Locus Ceruleus (LC) and the Dorsal Raphe Nucleus (DRN) are located in the Pons. TMN = tuberomammillary neurons; VLPO = ventro-lateral preoptic nucleus; MnPO = median nucleus, POMC = pro-opiomelanocortin, CART = cocaine and amphetamine regulated transcript.
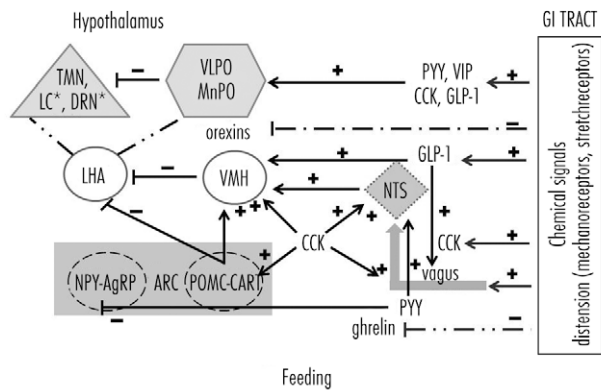
Figure 8.2. Afferent gastrointestinal signals controlling food intake and arousal: after feeding. Metabolic signs and distension of gastrointestinal (GI) tract inhibit the release of ghrelin and orexins. Cholecystokinin (CCK), glucose-like peptide (GLP), activate the arcuate nucleus (ARC) that through the expression of pro-opiomelanocortin (POMC) and cocaine and amphetamine regulated transcript (CART) activates the ventro-medial hypothalamus (VMH) and inhibits the lateral hypothalamic area (LHA). PYY-CCK-GLP-1-activated afferents vagus fibers, through the nucleus tractur solitarius (NTS), activate the VMH. The VMH in turn inhibits the LHA. The peptide-YY (PYY) suppress neuropeptide Y (NPY) in the ARC thus inhibiting the LHA. *The Locus Ceruleus (LC) and the Dorsal Raphe Nucleus (DRN) are located in the Pons. AgRP = agouti-related peptide.

protein-rich food should evoke less drowsiness than carbohydrates as it is known to increase the availability of tryptophan (Herrera *et al.,* 2011) but studies comparing different meals, did not find any difference in intensity of post-prandial drowsiness produced between protein- and carbohydrate-rich meals (Kim and Lee, 2009).

More promising have been the studies of the central pathway role of orexin neurons in the lateral hypothalamus. These neurons talk with the suprachiasmatic nucleus governing the circadian phase. They also increase cortical arousal and promote wakefulness, but their firing is suppressed by elevated blood glucose (Lowden *et al.*, 2004). Therefore orexins have been viewed as a barometer of energy homeostasis regulating both feeding and sleep/wakefulness.

It has also been shown that solid, but not equicaloric liquid, meal results in a decreased sleep onset latency in healthy volunteers (Orr *et al.*, 1997) suggesting that a post-ingestion mechanism rather than a cephalic stimulus is involved as initial trigger in mediating the phenomenon. Afferent signals arising from the lumen of GI tract are transmitted via various visceral afferent pathways (enteric, spinal and vagal) to the CNS. Vagal visceral afferent inputs may also play an important role in modulation of emotion, pain, satiety and immune response (Mayer *et al.*, 2006). In addition to meal constituents, data from animals studies suggest that visceral afferent feedback represents another mediating factor in facilitating post-prandial sleep. Kukorelli and Juhasz found that sleep waves increase in cats following electrical stimulation of the animal's duodenal mucosa (Kukorelli and Juhasz, 1976).

Studies assessing daytime sleepiness with standard tests, in healthy subjects showed that (1) sleep onset latency was significantly shorter after a caloric meal than after water (Orr *et al.*, 1997) and sham feeding (Harnish *et al.*, 1998), (2) the occurrence of after meal sleepiness was neither related to the fat composition of the test meal nor to the circadian variation in sleepiness (Wells *et al.*, 1998) and (3) the increase of sleepiness after food intake during daytime is superimposed on the influence of circadian rhythm and peak 3-4 hrs after meal ingestion (Lowden *et al.*, 2004). These results taken together with the observation that drowsiness may occur after an intravenous administration of CCK (Stacher *et al.*, 1979), support the hypothesis of brain-gut interactions in modulating sleep centres through, absorbed nutrients, GI neuro-hormonal and autonomic responses.

In addition to blood signals VMH and LHA receive signals from the GI tract through postprandially activated vagal afferents fibres and several neuropeptides and hormones. Feeding leads to reduction of ghrelin and orexins and increases the release of CCK, gastric 5-HT, gastric inhibitory peptides, GLP-1, VIP, pituitary adenylate cyclase-activating polypeptide, insulin, somatostatin, substance P, melatonin, secretin, PYY, leptin, gastrin releasing peptide (Figure 8.1). In addition to their local effects on GI tract, gut neuropeptides and afferent vagal pathways also modulate different brain functions. Some of the modulatory effects of gut neuropeptides and afferent vagal signals on the metabolic pathways of the brain overlap with those involved in sleep/ alert state. Gut peptides, PYY, CCK, leptin, 5-HT, and somatostatin released in response to gastric distension increase the central vagal stimulation occurring after meal through gut-activated vagal

afferents (Kim and Lee, 2009). The vagus nerve transfer satiety signals to the NTS which extends to the VMH, LHA and others hypothalamic areas (Figure 8.2).

However gut neuropeptides may also interrelate in the control of satiety and alertness independently by vagal activation by direct stimulation of the NTS, ARC, VMH and LHA (Figure 8.2). Insulin, VIP, PYY, CCK, somatostatin, leptin, and GPL-1 act directly through specific receptors on ARC, NTS, VMH and LHA and may also act directly on sleep centres. Intracerebral injection of VIP improves sleep in animals and intravenous infusion of VIP enhanced sleep in humans. Several animal studies indicate that CCK sleep-promoting and food-intake reducing effects are closely associated, presumably expressing different, yet related, manifestations of satiety. Furthermore satiety or metabolic state signal received by the hypothalamus through the blood or vagus nerve stimulation may directly or indirectly affect the POHA.

Also orexins appear to regulate both feeding and sleep axes promoting hunger and alertness. Cell bodies rich in orexins are found in the lateral hypothalamus. Connections between these cell bodies and inhibitory gaba-aminobutyric acid-ergic projections from the POHA have been implicated as a possible pathway by which orexins may regulate wakefulness (Bazar *et al.,* 2004). The link between gut response to food and alertness/sleepiness is also supported by the knowledge that melatonin, a pineal gland hormone, is also released by the gut and its release rises dramatically after meal (Bazar KA *et al.,* 2004).

8.3 Functional dyspepsia and postprandial drowsiness: pathophysiological mechanisms

Bi-directional brain-gut interaction plays an important role in the regulation of digestive processes in health and disease. It has been hypothesized that an alteration of brain-gut interactions may underlie the symptom generation in functional GI disorders and may be involved in the pathophysiology of various eating disorders. Even if the precise mechanisms underlying the symptom generation remains not completely understood, it is likely that the dysregulation in the complex interplay between events occurring in the GI tract lumen, the mucosa, the enteric nervous system and the CNS leads to alterations in sensation, motility and immune function (Mayer *et al.,* 2006).

In functional dyspepsia delayed gastric emptying, impaired gastric accommodation and visceral hypersensitivity have been implicated in the aetiology of symptoms (Figure 8.3), but so far the above mentioned pathophysiological abnormalities failed to establish a clear-cut association between symptoms and specific function abnormalities and often-similar studies provided contrasting findings (Boeckxstaens *et al.,* 2001; Piessevaux *et al.,* 2003; Talley *et al.,* 1989). Indeed investigations performed while patients are symptom free may miss their underlying pathophysiological mechanisms because as the symptoms, they may wax and wane over time (Agreus *et al.,* 1995). To complicate the matter, in addition to the well-known long-term variability, it has been shown that dyspeptic symptoms may wax and wane even over a short period of time
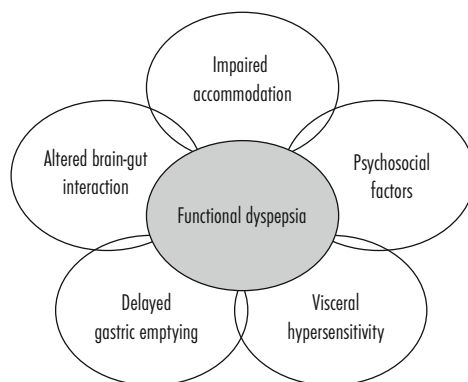
Figure 8.3. Proposed pathophysiological mechanisms involved in functional dyspepsia.

(Pallotta *et al.,* 2006). Finally despite symptoms are often related to food ingestion few studies have assessed the relationship between the occurrence of GI symptoms after meal ingestion and gastric functions (Boeckxstaens *et al.,* 2001; Pallotta *et al.,* 2006; Piessevaux *et al.,* 2003; Ricci *et al.,* 1987) reporting not univocal results.

Lumen distension is regarded a major stimulus for the induction of GI symptoms in patients with FGID, including IBS and FD (Ong *et al.,* 2010). Impaired accommodation of the proximal stomach to a meal has been found in approximately 40% of FD patients and it was associated with early satiation.

Ricci *et al*. firstly (Ricci *et al.,* 1987) and others subsequently (Delgado-Aros *et al.,* 2004; Hausken and Berstad, 1992; Troncon *et al.,* 1994) described in patients with FD a distended fasting antrum and an increased post-prandial antral volume compared to healthy controls suggesting that an impaired motor function of the distal stomach is present in a subgroup of patients with FD. A study reported the temporal association between the onset of usual postprandial GI symptoms, antral distension and antral volume increase (Ricci *et al.,* 1987) in the majority (71%) of patients. A subsequent study reported only an association between bloating and antral distension in a subgroup of patients (Hausken and Berstad, 1992), and a more recent study (Pallotta *et al.,* 2006) did not find any association between GI complaints with antral distension or with gastric emptying. Conversely the authors found a close association between after meal drowsiness with antral distension and, confirming a preceding study (Pallotta *et al.,* 2005), with delayed gastric emptying. Postprandial drowsiness reported in this study by 17% of patients refers to a sensation regarded to be bothersome enough to interfere with the daily activities and was not related to clinically apparent sleep disturbances.

It has been shown that in healthy subjects postprandial drowsiness is related to younger age and to a greater food intake compared to older subjects (Parker *et al.,* 2004). In the mentioned study healthy controls, although significantly younger than FD patients, did not report any symptom. It would therefore appear that, differently from healthy controls, drowsiness reported by older

dyspeptic patients was not related to sleepiness nor to physiological change of after meal sleep latency, nor to meal composition.

Differently from the usual dyspeptic symptoms that occur within the first postprandial hour, drowsiness is a late postprandial complain occurring significantly later than GI symptoms thus confirming the data in healthy subjects in whom the objective signs of sleepiness peak 3 hr after the meal (Lowden *et al.,* 2004; Wells *et al.,* 1997, 1998). The comparative assessment of the relationship between gastric emptying, antral volume variations and postprandial symptoms in symptomatic versus asymptomatic dyspeptic patients and healthy subjects showed that the antral volume reached its maximal value soon after the end of meal ingestion and subsequently decreased throughout the observation period in both controls and FD patients (Figure 8.4) (Pallotta *et al.,* 2006). However independently from the concomitant presence of GI dyspeptic symptoms, FD patients showed an antral volume greater than healthy controls confirming the presence of an altered intragastric meal distribution in FD patients (Hausken and Berstad, 1992; Troncon *et al.,* 1994). The increased antral volumes found in these patients, may reflect hypotonia of the antral muscular wall or intraluminal distension secondary to gastric retention or to an overload caused by an impaired accommodation of the proximal stomach, or an increased duodenogastric reflux. However the overdistension of the antrum occurred late after the meal and thus it appears independent from an increased distribution of gastric contents in the antrum due to altered motor function of the proximal stomach that usually takes place early after-meal.
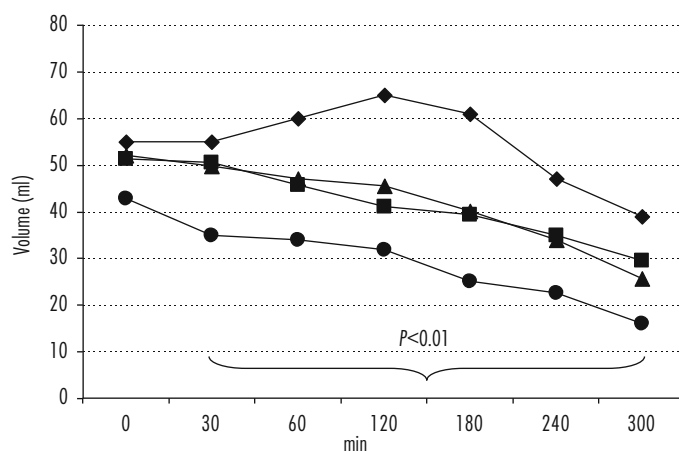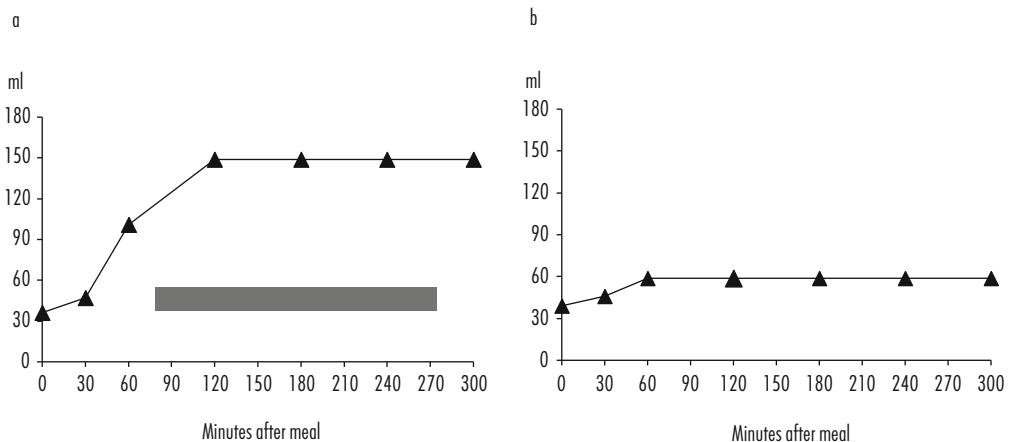

Figure 8.4. Postprandial gastric antral volume variations according the presence or absence of symptoms during the test meal. Antral volume measurements (ml) immediately (0) at 30 and at 60 min intervals, after the end of the ingestion of a standard meal, in controls (circle), in asymptomatic patients (square), in symptomatic patients with usual dyspeptic symptoms (triangle) and in symptomatic patients also referring to drowsiness (diamond). The antral volume was greater in dyspeptic patients than in healthy controls ($P<0.01$), independently from the concomitant presence of GI dyspeptic symptoms.

Notably postprandial drowsiness was the only of GI and extra-GI symptoms to be associated with antral volume variations. In patients with postprandial drowsiness antral volume reached the maximal value 2 hrs after the meal and did not show a progressive decrement throughout the observation period (Figure 8.4). The occurrence of postprandial drowsiness appears to be time-related to antral distension being its onset (1) associated with the degree of time-related variation of the increase of antral volume rather than the antral volume *per se* and (2) preceded by antral distension (Figure 8.5a and b). The onset of postprandial drowsiness is preceded by an increment of antral distension and the duration of the symptom appears to be related to persistence of antral distension. These data support the hypothesis that sustained antral distension activates a peripherally release of neuroendocrine substances of GI origin that, in FD patients, affect the state of consciousness directly or activating vagal nerve afferences. Furthermore distension of the stomach activates, *per se*, stretch receptors and mechanoreceptors that transmit satiety signals to the brain through vagal nerve afferents.

It has been widely debated whether a delayed gastric emptying is a relevant factor in causing dyspeptic symptoms. A previous study reported a delayed gastric emptying in 41% of the patients and a rapid initial gastric emptying in 43% of them that was associated with higher symptom score after a challenge meal (Delgado-Aros *et al.,* 2004). Thus it would appear that a delayed gastric emptying *per se* does not play any role in the origin of the usual dyspeptic symptoms. Two recent studies (Pallotta *et al.,* 2005, 2006) have shown that FD patients referring to postprandial drowsiness have a greater probability to have delayed gastric emptying than controls and dyspeptic

Figure 8.5. Time-relationships between the onset of drowsiness and after meal antral volume variations. (a) Patient referring to postprandial drowsiness during the study period. The increase of antral volume expressed as maximal antral volume value reached between the current and the previous measurement, precedes the onset of drowsiness. The drowsiness on the average starts 70 min after the end of meal ingestion (time 0) and ends on the average 270 min after the end of meal ingestion.(b) Patient not referring to symptoms during the study period. Horizontal line: mean duration of the drowsiness.

patients without post-prandial drowsiness. It would therefore appear that the two conditions are associated with the onset, and the persistence of, postprandial drowsiness in this subgroup of FD patients even if it is not known the relative role, if any, played by delayed gastric emptying and antral distension, either alone or in combination, in the occurrence of the symptom.

Several substances, released as result of antral distension and/or delayed gastric emptying might be involved in mediating postprandial drowsiness in FD patients. Amongst GI peptides ghrelin is produced mostly in the stomach. Plasma ghrelin peaks before meals and then decreases to progressively increase to another peak just before the next meal (Näslund and Hellström, 2007). The effect of ghrelin on feeding behaviour are mediated via the ARC and NTS and partially through the vagal afferent loop (Figure 8.2). In addition ghrelin is a ligand for the growth hormone release factor that is known to promote sleep in humans. The sustained antral distension and the prolonged passage of contents in the duodenum, due to the delayed gastric emptying, might keep low the plasma level of ghrelin, inducing indirectly via ARC and NTS inhibition of LH, and thus drowsiness.

It has been shown that CCK inhibits food intake and induce sleepiness, although a concomitant gastric preload is needed to achieve satiety (Näslund and Hellström, 2007). It has also been reported a relationship between decrease of plasma level of CCK, hunger and decrease of postprandial fullness. Postprandial fullness is a common sensation referred either by FD patients and by healthy controls and it has been reported that perception of fullness is a useful predictor of food intake (Parker *et al.,* 2004). The presence of delayed gastric emptying in FD patients complaining of drowsiness may determine a continuous duodenal release of CCK that directly, or activating vagal afferents, may in turn promote drowsiness and fullness.

Also orexins may be involved in mediating the phenomenon since its release is inhibited by antral distension (Figure 8.2).

Several studies suggest a possible role of serotoninergic signalling in the pathogenesis of dyspeptic symptoms (Gershon and Tack, 2007). Serotonin synthesized by enterochromaffin cells in the GI mucosa and by myenteric neurons is excreted primarily into the lamina propria in response to intraluminal pressure. Released 5-HT acts on 5-HT receptors on the mucosal projection of primary afferent neurons, including extrinsic nerve which transmit sensation to the CNS. In FD patients the increase availability of 5-HT may contribute to the occurrence of drowsiness.

Recently it has been shown that dietary manipulation, using diets that differed only in FODMAPs content induce GI and systemic symptoms including sleepiness in IBS patients (Ong *et al.,* 2010). In this study dietary FODMAPs induce prolonged hydrogen production in the intestine that is greater in IBS patients compared to healthy controls and influence the amount of methane produced. The intraluminal gas production may in turn alter the volume of contents within the intestinal lumen leading to luminal distension. Notably the diet with an high contents of FODMAPs did induce in healthy, non-IBS subjects, exclusively a passage of excessive amounts of wind, while in IBS patients induce heartburn, nausea, and lethargy that are not typical symptoms of IBS.

Therefore postprandial drowsiness appears to be a systemic symptom common to different FGID. The results of these studies suggest that luminal distension of any tract of the digestive system may induce sleepiness in FGID patients, thus supporting the hypothesis of an underlying common mechanism of altered brain-gut interaction.

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Summary points

- Eating and sleep disturbances are associated with patients with eating disorders/obesity, with night eating syndromes and with sleep problems.
- General practitioners should pay attention to the possibility of a relationship between sleep and eating disturbances; this association may begin early in life.
- Studies in university students show that eating and sleep disturbances are interrelated.
- Bulimic behaviours are particularly associated with sleep disturbances.
- Connections between a lower body mass index (BMI) and sleep difficulties are found in university students.
- University Counseling Services may start to consider eating disorders in their prevention programs to reduce their consequences on student's daily function, academic performance and well being (for instance, by incorporating sleep habits and eating disturbances in the universities' clinical assessments).
- Possible causes for the interrelation between sleep and eating disturbances might include bio-psycho-social factors/mechanisms; this study explores some of these.
- Future research should be done through longitudinal studies, the inclusion of objective measures of sleep difficulties/BMI, incorporating factors that may determine/mediate the eating/sleep disturbances association.

9. Sleep disturbances and eating behaviours in undergraduate students

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Abstract

There is an increasing recognition that sleep and eating behaviours are related. The evidence comes both from sleep and eating disorders settings and from empirical findings with clinical and community samples. The aim of the present paper is to analyse on the relationship between sleep and eating behaviour in university students. Two types of clinical data supporting the association between disordered eating and sleep disturbances are critically reviewed: (1) syndromes combining night eating and sleep problems; and (2) co-morbidity between sleep disorders and eating disorders/obesity. The research on the relationship between body mass index (BMI) and sleep is also summarised. The contribution of neurobiological/psychological mechanisms on the association between sleep difficulties and eating disturbances/BMI is explored. Some potential implications, for the clinical management of these disturbances or even their prevention, are discussed.

Keywords: sleep; eating disturbances; biological/psychological mechanisms; undergraduate students

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Abbreviations

AN	Anorexia nervosa
AN-B/P	Anorexia nervosa binge-eating/purging subtype
AN-R	Anorexia nervosa restrictive subtype
BB	Bulimic behaviours
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
BN-NP	Bulimia nervosa non-purging subtype
BN-P	Bulimia nervosa purging subtype
DC	Diet concerns
DIS	Difficulties in initiating sleep
DMS	Difficulties in maintaining sleep
EAT	Eating attitudes test
ED	Eating disorders
ED-NOS	Eating disorders not otherwise specified
NEDS	Night eating/drinking syndrome
NES	Night eating syndrome
REM	Rapid eye movement
SPE	Social pressure to eat
SRED	Sleep-related eating disorder

9.1 Introduction

Empirical and clinical findings indicate that eating disturbances and sleep are associated. Sleep restriction has an important role at triggering metabolic disorders, such as glucose metabolism dysregulation, a risk factor for both insulin resistance and diabetes and to diminished leptine sensitivity (that causes overeating and may lead to obesity) (Adam and Epel, 2007).

Two types of clinical data support the association between eating and sleep disturbances: syndromes with combined night eating and sleep problems, and sleep disorders or ED where high co-morbidity between the two is observed. Empirical studies in the general population also revealed that eating behaviour disturbances and sleep complaints are associated. Experimental studies on starvation, performed in 1950 by Keys and colleagues, showed that severe dietary restriction in healthy young adult males can lead to severe physical and psychological complaints, including food preoccupation, binge eating, sleep disruption and decreased need for sleep. On the other hand, sleep restriction/insufficient sleep are associated with increased appetite and food preferences for carbohydrates and fat food in healthy volunteers (Nedeltcheva *et al.,* 2009), and may lead to weight gain/obesity (Patel and Hu, 2008).

This suggests that eating and sleep problems may cluster together throughout a continuum from less severity, such as eating and sleep disturbances in community subjects, to more severe manifestations, such as eating and sleep difficulties in subjects with obesity, in patients with ED, combined eating and sleep disturbances or sleep disorders.

The aim is to focus specifically on the relationship between sleep and eating behaviour in university students, and to provide an integrative view of this association in community and clinical settings. Possible contributors and clinical implications are analysed.

9.2 Sleep and eating disorders

ED are characterised by severe eating behaviour disturbances and nutritional deviances. The two ED major categories are AN and BN. When criteria for the above diagnostic categories are not completely satisfied, the ED-NOS must be used (DSM-IV-TR, 2000). The BED is considered a subtype of ED-NOS and is also described, in DSM-IV-TR, as a diagnostic proposal requiring further research. The BED is characterised by recurrent binge eating episodes in the absence of the extreme weight-control behaviours, as seen in BN (Table 9.1).

Table 9.1. Anorexia nervosa and bulimia nervosa diagnostic and subtypes characteristics, distinct features and communalities.

Anorexia nervosa	Bulimia nervosa
Maintenance of excessively low body weight	Recurrent episodes of binge eating
Intense fear of gaining weight or becoming fat	A lack of control over feeding
Loss of sexual interest or potency in men (ICD-10, 1992) and amenorrhea in women (DSM-IV-TR, 2000; ICD-10, 1992)	Inappropriate weight gain compensatory behaviours
Subtypes (DSM-IV-TR, 2000)	Subtypes (DSM-IV-TR, 2000)
• restrictive (AN-R): characterised by excessive caloric restriction and exercise only	• purging (BN-P): purgative behaviours observed during the current episode of BN
• binge-eating/purging (AN-B/P): characterised by overeating or purging.	• non-purging (BN-NP): no purgative behaviours observed during the current episode of BN
AN communalities: patients maintain severe caloric deficits, necessary to continue their low weight	BN communalities: patients usually maintain their weight in a normal range or may even gain weight
Communalities of both AN and BN: the morbid fear of becoming fat, the over-evaluation of body shape and weight and the unduly influence of weight and shape in self-evaluation.	

AN-R = anorexia nervosa restrictive subtype; AN-B/P = anorexia nervosa binge-eating/purging subtype; BN-P = bulimia nervosa purging subtype; BN-NP = bulimia nervosa non-purging subtype; BN = bulimia nervosa; AN = anorexia nervosa.

Given the nutritional aspects of the ED diagnostic categories and subtypes, it will be expected that the associated sleep disturbances are different. Based on clinical observations of AN patients sleeping habits, Dally (1969) suggested that sleep disturbances in AN are related to the starvation, to peculiarities of diet and to the degree of patient emaciation. 'The most usual symptom is waking early in the morning'. However 'some patients will sleep lightly and waken several times during the night' (Dally, 1969: 8, 35). AN-B/P patients and bulimics (BN, BED) may also have nocturnal sleep wakes to overeat.

Objective studies of sleep characteristics in AN patients, when compared to normal controls, showed lower sleep efficiency, lengthier awakenings and reduced REM sleep (Delvenne *et al.,* 1992). Levy and colleagues (1987, 1988), found that AN showed reduced slow wave sleep and increased stage 1 sleep.

Although BN patients may report insomnia, more often they describe hypersomnia after binges. They usually binge in the evening/night and tend to fall asleep, and to wake up in the morning about one hour later than healthy controls (Latzer *et al.,* 1999). However, some studies, using objective measures of sleep did not replicate these findings and showed no significant differences on sleep characteristics between AN or/and BN subjects and healthy controls (Lauer *et al.,* 1990). Methodological differences between these studies on the objective characteristics of sleep in ED patients might explain the different results.

There are some discrepancies between objective and subjective results on sleep evaluation, as the latter report a higher incidence of sleep disturbances. A recent transversal study of Kim and colleagues (2010), using self-reported sleep measurements, explored the difficulties of falling asleep, midsleep awakenings, early morning awakening, parasomnia and hypersomnia, across ED categories and subtypes, in a sample of 400 Korean female ED patients, aged between 13-49 years (mean age=23.15 years, SD=4.98). Sleep disturbances were reported by 50.3% of ED patients, most common being difficulties in initiation (32.5%) and maintenance of sleep (17.8%). Although there was no significant differences between AN and BN patients in global sleep disturbance prevalence (58.3% vs. 57.3%), those with binge-eating/purging subtypes had significantly more sleep disturbances (56.8% vs. 34.1%), irrespective of having an AN/BN diagnosis. Both AN-B/P and BN-P were associated with more eating disturbances and a higher prevalence of difficulties in initiating sleep, early morning awakening, parasomnias and hypersomnia than AN-R, BN-NP, and EDNOS. Moreover, a higher prevalence of midsleep awakenings were observed in AN-B/P subjects compared to AN-R, BN-NP, and EDNOS; and in BN-P subjects compared to AN-R and BN-NP. These findings suggest a strong association between sleep disturbances and disordered eating, particularly in bulimic/purgative behaviours.

The AN sleep patterns alterations may be due to endocrine and metabolic disturbances related to the pursuit of thinness, to nutritional deficits, starvation and consequent weight loss. Moreover, the under-feeding, overeating and purgative behaviours, the frequent body weight fluctuations in subjects with bulimic behaviours may cause rapid metabolic and neuroendocrine changes that lead to abnormal sleep patterns.

9.3 Night eating disorders/syndromes

The association between eating behaviour disturbance and sleep difficulties is supported by the SRED, NES, and the NEDS, which was removed from the International Classification of Sleep Disorders, 2nd revision (American Sleep Disorders Association, 2005) (Table 9.2).

Table 9.2. Distinct characteristics and communalities of the night eating syndrome (NES), night eating/drinking syndrome (NEDS) and sleep-related eating disorder (SRED).

Syndromes/disorders	Main characteristics
SRED	• state of partial arousal from sleep with rapid episodes of ingestion of food • the episodes were described as 'out of control' (e.g. may include eating in a sloppy manner, ingestion of unusual combinations of food or inedible substances) • the memory for the episode can be of partial or of total amnesia, in the following morning

NES[1]	• time-delayed pattern of eating relative to sleep, in which most of the food is consumed in the evening and night.
	• the core criteria are:
	  1. evening hiperfagia, and/or nocturnal awakenings involving consumption of food
	  2. awareness preservation during nocturnal awakenings with ingestion of food.
	• the additionally criteria are:
	  1. morning anorexia (morning lack of desire to eat and/or breakfast omitting)
	  2. a strong desire or urge to eat between dinner and sleep initiation and/or upon awakening at night from sleep
	  3. sleep onset and maintenance insomnia
	  4. the belief that one must eat in order to get to sleep
	  5. depressed or lowering of mood in the evening and at night
	  6. distress or functioning impairment as a result of symptoms
	  7. the syndrome duration for at least 3 months
	  8. the disorder is not secondary to another medical or psychiatric condition

NEDS[2]	• recurrent episodes of awakenings with inability to return to sleep without eating or drinking • maintenance of full awareness during the episodes and no subsequent amnesia • no evidence of any psychiatric (e.g. bulimia) or medical conditions (e.g. hypoglycemia) or other sleep disorder (e.g. primary insomnia by eating to 'kill time').

Communalities: the patients wake up during the night to eat or to binge eat

[1] These NES criteria were recently proposed by the International NES Working Group, Minneapolis, 2008 (Allison *et al.*, 2010).
[2] From the International Classification of Sleep Disorders, 2nd revision (American Sleep Disorders Association and ASDA, 2005).

A common feature of these disorders is that patients wake up during the night to eat or to binge eat. Night eating can occur in normal weight, overweight and obese subjects, in subjects with eating disorders (AN-B/P; AN-R with binge eating at night, BN; BED), or in subjects with a sleep disorder.

In obese patients NEDS prevalence varies between 8% and 42% (Ceru-Bjork *et al.,* 2001; Hsu *et al.,* 1996), while NES prevalence, among those undergoing a weight reduction treatment, generally range from 6% to 15% (Adami *et al.,* 1999; Kuldau and Rand, 1986).

Kim and colleagues (Kim *et al.,* 2010) found ED comorbidity with parasomnia in 10.9% of AN-B/P patients, 0% AN-R, 10.1% BN-P, 7.9% BN-NP, and 3.1% of ED-NOS. Tzischinsky and Latzer (2004) found that 5% of all referrals to an ED clinic during three years met diagnostic criteria for NES, and that this syndrome prevalence was 16% in patients with BED, 9% in patients with BN and 0% in patients with AN-B/P. Winkelman and colleagues (1999) found that 16.7% of ED outpatients and 8.7% of ED inpatients had a NSRED.

Current and lifetime eating disturbances were also found in subjects who were referred to sleep disorders clinics. In these patients, the prevalence of SRED ranges between 0.5% and 5% (Winkelman *et al.,* 1999) and NEDS prevalence varies between 5% (Spaggiari *et al.,* 1994) and 6% (Manni *et al.,* 1997).

Night eating can also occur in the general population. Bjorvatn and colleagues (2010) in an adult population-based study found that the lifetime sleep related eating was 4.5%. In undergraduate students, NSRED prevalence varies between 0.6% (Goldin and Rosin, 1997) and 4.7% (Winkelman *et al.,* 1999).

9.4 Sleep disturbances and eating behaviour in undergraduate students

Research on the association between sleep and eating disturbances in community based populations is scarce. There are only four studies specifically designed to examine the co-morbidity between sleep problems and disordered eating behaviours in the community (Table 9.3).

One of these was conducted by Seigel and colleagues (2004) in a sample of 726 young Sweden females (age range=18-23 years, BMI=21.7, SD=3.0; 16.4% overweight; 13.2% low weight; 1.8% BMI<17.5). It was found that frequent attempts to reduce weight, body image dissatisfaction, feelings of being overweight, fear of becoming fat, binge eating, and the impulse to vomit after eating were significantly associated with difficulties in maintaining sleep and with non-restorative sleep (Table 9.3).

Soares and colleagues (2011) explored the association between sleep disturbance and eating behaviour in a sample of 870 students from Dentistry and Medicine Faculties of Coimbra University (544 females, 62.5%), aged between 17-25 years (mean age=19.59 years; SD=1.61)

Table 9.3. Studies designed to examine the associations between sleep problems and disordered eating behaviours in community and in student samples. Main findings concerning the associations between eating/ body mass index and sleep disturbances.

Study	Design	Sample	Main findings
Seigel *et al.*, 2004	transversal	n=726 females community sample age range=18-23 yrs Sweden	DMS and non-restorative sleep were associated with the attempts to reduce weight, body image dissatisfaction, feelings of being overweight, fear of becoming fat, binge eating, and the impulse to vomit after eating.
Soares *et al.*, 2011	transversal	n=870 undergraduate students (544 females) age range=17-25 yrs Portugal	BB were predictors of global sleep disturbance and DIS (in both genders). In males, BB were also significant predictors of DMS. BB and SPE are significant predictors of the likelihood of having insomnia in both genders.
Lopes, 2011	transversal	n=465 undergraduate students (330 females) age range=17-26 yrs Portugal	BMI was not significantly associated with habitual sleep duration and sleep debt in both genders. BMI was negative and significantly associated with sleep needs in males. BMI was not associated with sleep measures in females. *Females subsample* (n=330): Sleep debt and poor self-reported psychological health were significant predictors of BB, controlling for the effect of BMI. The association between short sleep duration and DC and between sleep debt and global eating disturbance were completed mediated by poor self-reported psychological health.
Bos *et al.*, unpublished data	longitudinal	baseline n=870 undergraduate students age range=17-25 yrs T1 n=592 T2 n=305 Portugal	Baseline BB and SPE were predictors of DIS at T1 and T2, of overall sleep disturbance and DMS at T1. Conversely, DIS at baseline were significant predictors of BB at T1 and T2. The ability of sleep difficulties to predict DC, global eating disturbances and SPE were less consistent over time. DIS are predictive of low BMI over time in a sample of both genders. However, low BMI was not a predictor of sleep difficulties over time.

DIS = difficulties in initiating sleep; DMS = difficulties in maintaining sleep; BMI = body mass index (kg/m^2); BB = bulimic behaviours; DC = diet concerns; SPE = social pressure to eat; T1=one year after baseline; T2=two years after baseline.

(Table 9.3). To measure eating disturbances the Portuguese version of the EAT-40 was used (Soares *et al.,* 2004).

The EAT is a self-report instrument widely used in the field of ED. It evaluates three dimensions: (1) DC, this includes concerns about food and being thinner, self-control over eating, and engagement in dieting and physical exercise to burn calories; (2) BB, which measures persistent preoccupations with food, overeating episodes and purgative behaviour; and (3) SPE, which evaluates perceived pressure from others to eat/gain weight. The EAT-40 dimensions in males were DC, BB/binge eating, BB/purgative behaviours, SPE and pleasure to eat (associated with the pleasure of eating with others, out/in restaurants, and to try new foods). To improve comparability between genders, the BB/binge eating scores and BB/purgative behaviours scores were summed up to provide a global BB measure in males. The EAT-40 total score is used to provide a global measure of disordered eating attitudes and behaviours. BMI (kg/m^2) was calculated from self-reported weight and height (Soares *et al.,* 2011). Two items were used to assess DIS and in maintaining sleep (DMS). A sleep disturbance index was calculated by summing DIS and DMS scores.

Total sample BMI mean score was 21.54 (SD=2.53). There were 7.9% subjects under weighted (BMI<18.5) and 8.6% over weighted (BMI≥25). Only 1.1% students had a BMI≤17 (all of them were females) and 0.6% subjects had a BMI≥30 (all of them were males). The total EAT-40 mean score for females was 54.03 (SD=16.17) and there were 8.4% females who scored one standard deviation above the mean. The total EAT-40 mean score in males was 43.83 (SD=12.75) and there were 4.9% males who scored one standard deviation above the mean.

Significant correlations were observed, both in males and females, between eating behaviour disturbances, particularly BB and SPE, and global sleep difficulties, DIS and DMS. Also in females and males, BB were predictors of global sleep disturbance and DIS, even after controlling for age and BMI, when appropriate. In males, BB were also significant predictors of DMS. The association between DC and sleep disturbances is less consistent in females and is not significant in males. The females and males with insomnia symptoms (subjects that scored DIS and/or DMS items as 'often', 'very often', and 'always') have significantly more eating disturbances when compared to a control group of good sleepers (subjects reporting DIS and DMS items as 'never' or 'rarely'). Moreover, BB and the perception that others exert pressure to eat more are significant predictors of the likelihood of having insomnia in both genders.

The third study, with a cross-sectional design, examined the association between sleep debt, disordered eating attitudes and behaviours and BMI, in a sample of 465 undergraduate medical students (330 females) from Coimbra University (Lopes, 2011). Eating attitudes and behaviours were assessed with the EAT short version (EAT-25) (Pereira *et al.,* 2011). Self-reported current body weight and height were used to calculate BMI (kg/m^2). Sleep debt was evaluated subtracting self reported sleep needs ('How many hours do you need to sleep to feel good and function well during the day?') from habitual sleep duration ('How many hours do you usually sleep per night?'; both with 9 alternative replies ranging from 5 hrs or less to 11 hrs or more).

Self-reported health was measured with two questions: (1) Generally, what has your physical health been like, (2) Generally, what has your psychological (mental) health been like. Responses were 'very poor', 'poor', 'neither good nor poor', 'good', 'very good'.

The total sample BMI mean score was 21.54 (SD=2.49). There were 11.0% subjects under weighted (BMI<18.5) and 6.2% over weighted (BMI≥25). Only 1.2% students had a BMI≤17 (all of them were females) and 0.6% subjects had a BMI≥30 (one female and two males).

Most students had good mental and physical health. There were only 13 subjects who reported poor/very poor physical health (1.5% females; 1.1% males) and 24 subjects who reported poor mental health (1.9% males; 3.2% females).

No significant associations were found between BMI, habitual sleep duration and sleep debt in both genders. Only in males BMI was negatively and significantly associated with sleep needs: males who need to sleep less than 6 hrs to feel and function well have a higher BMI than those who need to sleep 7-8 hrs per day or those who need to sleep more than 8 hrs. In females a higher BMI was associated with poor self-reported physical health and higher eating disturbance, particularly BB (Lopes, 2011). Findings not published from this sample also revealed that BMI was associated with snoring and dozing off/falling asleep at morning classes.

Lopes (2011) only studied the association between sleep debt and disordered eating behaviour in the female sub-sample (n=330; mean age=18.72 years; SD=1.26), because the psychometric characteristics of the Portuguese version of the EAT-25 have been analysed only in females (Pereira *et al.,* 2011). The total EAT-25 mean score was 4.44 (SD=5.76; range=0-30) and there were 13 (4.6%) females who scored above the cut-off 19. The findings from this study suggest an association between sleep debt and eating behaviours disturbances, particularly BB in females. Even after controlling for the effect of BMI, sleep debt and poor psychological health remained significant predictors of BB. Although the association between short sleep duration and DC and between sleep debt and global eating disturbance were also significant, they were completed mediated by poor self-reported psychological health. Moreover, sleep debt and lower BMI (but not psychological health) significantly contributed to the perception that others make pressure to eat more (Lopes, 2011).

However, these studies are cross sectional and more informative longitudinal studies are necessary to establish the causal relationship between sleep and eating problems. Bos and colleagues (unpublished data), using the sample of Soares and colleagues (2011) transversal study, performed a two years longitudinal study. The students were again requested to complete the same instruments as described above. Out of 870 students who participated at baseline, 592 (65%) and 305 (48.5%) completed the same measures one year (T1) and two years later (T2), respectively (Table 9.3).

Interestingly, the prospective findings showed that the relationship between sleep difficulties and eating behaviours operates in both ways. BB and SPE were predictors of DIS over time (T1, T2),

and of overall sleep disturbance and DMS one year after (T1). Conversely, DIS at baseline were significant predictors of BB over time (T1, T2). The ability of sleep difficulties to predict DC, global eating disturbances and SPE were less consistent over time (Table 9.4 and 9.5).

Table 9.4. Regression analyses: BMI, DIS, DMS as predictors for EAT total and EAT factors at Time 1 and Time 2 of the study.

Predictors	Time 1			Time 2		
	β	R^2 change F	P	β	R^2 change F	P
EAT total						
BMI	0.096	0.009	3.441	0.064	0.163	0.027	5.037	0.026*
DIS	0.090			0.123	0.252	.		0.002**
DMS	0.094			0.107	0.121			0.127
		0.025	4.689	0.010**		0.107	11.172	<0.001**
DC						
BMI	0.094	0.009	5.102	0.024*	0.168	0.028	8.288	0.004**
DIS	0.065			0.167	0.150			0.026*
DMS	0.034			0.473	0.081			0.228
		0.008	2.210	0.111		0.042	6.238	0.002**
BB						
BMI	-0.053	0.003	1.625	0.203	-0.055	0.003	0.899	0.344
DIS	0.185			<0.001**	0.231			<0.001**
DMS	0.028			0.542	0.011			0.864
		0.040	12.088	<0.001**		0.056	8.753	<0.001**
SPE						
BMI	-0.380	0.144	97.75	<0.001**	0.050	0.003	0.506	0.478
DIS	0.209			<0.001**	0.211			0.317
DMS	0.025			0.582	0.655			0.023*
		0.050	15.285	<0.001**		0.053	5.565	0.004**
BMI						
DIS	-0.116			0.015*	-0.215			0.001**
DMS	0.044			0.360	0.094			0.155
		0.010	3.021	0.050*		0.034	5.301	0.005**

BMI = Body Mass Index; DC = diet concerns; DIS = difficulties initiating sleep; DMS = difficulties maintaining sleep; BB = bulimic behaviour; SPE = social pressure to eat; EAT = eating attitudes test.
*P<0.05; ** P<0.01.

Table 9.5. Regression analyses: BMI, EAT factors as predictors of SDI, DIS and DMS.

Predictors	Time 1				Time 2			
	β	R^2 change	F	P	β	R^2 change	F	P
Sleep disturbance index								
BMI	-0.017	0.000	0.159	0.690	-0.062	0.004	1.161	0.282
DC	-0.026			0.577	0.036	.		0.593
BB	0.173			<0.001**	.114			0.101
SPE	0.154			<0.001**	.154			0.010*
		0.061	12.531	<0.001**		0.054	5.645	0.002**
DIS								
BMI	-0.048	0.002	1.346	0.246	-0.075	0.006	1.686	0.195
DC	-0.023			0.620	0.048			0.479
BB	0.187			<0.001**	0.151			0.031*
SPE	0.147			0.001**	0.123			0.038*
		0.065	13.263	<0.001**		0.060	6.293	<0.001**
DMS								
BMI	0.028	0.001	0.472	0.492	-0.040	0.002	0.489	0.485
DC	-0.023			0.629	0.065			0.340
BB	0.104			0.032*	0.096			0.173
SPE	0.117			0.006**	0.122			0.041*
		0.028	5.457	0.001**		0.044	4.539	0.004**

BMI = Body Mass Index; DC = diet concerns; DIS = difficulties initiating sleep; DMS = difficulties maintaining sleep; BB = bulimic behaviour; SPE = social pressure to eat; EAT = eating attitudes test.
*P<0.05; ** P<0.01.

As previous studies showed that socially-prescribed perfectionism was associated with sleep disturbances (Azevedo *et al.,* 2010a), and that socially-prescribed perfectionism and self-oriented perfectionism were associated with eating disturbances (Macedo *et al.,* 2007; Soares *et al.,* 2009), Bos and colleagues decided controlling for the effect of these perfectionism dimensions yet (Bos *et al.,* unpublished data). The results remained significant, indicating that eating disturbances (BB, SPE) are significant predictors of global sleep disturbances and DIS one year after baseline, and BB tend to contribute to the explanation of DIS variance two years after. Conversely, DIS remains a significant predictor of SPE and BB one year after baseline and tends to contribute to the explanation of BB variance two years after (Bos *et al.,* unpublished data).

Regarding the association between BMI and sleep disturbances, results showed that DIS are predictive of low BMI over time in a sample of both genders (Bos *et al.,* unpublished data). However the reciprocal association was not observed: low BMI was not a predictor of sleep difficulties over time (Bos *et al.,* unpublished data) (Table 9.4 and 9.5).

In summary, the transversal studies in student samples, revealed consistent associations between BB, SPE and sleep disturbances (mainly DIS) in both genders (Soares *et al.,* 2011) and sleep debt in females (Lopes, 2011). Additionally, the likelihood of experiencing insomnia was associated with global eating disturbances, BB, and SPE in males and females (Soares *et al.,* 2011). The association between sleep difficulties and DC are less consistent and only observable in females (Soares *et al.,* 2011). In this context, it is noteworthy the original contribution of findings from Bos and colleagues longitudinal study suggesting that the causality between eating disordered behaviours and sleep disturbances is bidirectional and can occur in healthy subjects. Thus, the BB and SPE are risk factors for sleep difficulties over time, and conversely sleep difficulties are risk factors for long term BB (Bos *et al.,* unpublished data). Therefore, these findings suggest that eating and sleep disturbances relationship is reciprocal and may cluster together in university students.

The studies in student samples showed no significant associations between BMI and habitual sleep duration and sleep debt in both genders (Lopes, 2011), but DIS can predict low BMI over time in both genders (Bos *et al.,* unpublished data). These results were not in accordance with the main findings from literature, which indicated an association between short or short and long sleep duration and overweight/obesity (Patel and Hu, 2008). The inverse association between DIS and BMI is a new finding and suggest that non-clinical samples may behave in a similar way to clinical populations (Dally, 1969).

9.5 Putative factors

9.5.1 Neurobiologic mechanisms

Over the last decade, our understanding of the circuits involved in sleep, arousal and appetite regulation, has changed dramatically. We will only focus on a few central aspects of the complex hypothalamic machinery underlying the interface between sleep-wake cycle, feeding behaviour and arousal/stress reactivity.

The lateral hypothalamic area plays a key role in the regulation of ingestive behaviour, and sleep-waking regulation, with some peptides being expressed in the brain only in this area: and orexins A and B (also known, respectively as hypocretins 1 and 2) (Sakurai *et al.,* 1998). The melanin concentrating hormone and orexin neurons send projections to a wide variety of structures including locus coeruleus, the dorsal and median raphe nuclei, and the tuberomammillary nucleus, which together constitute an ascending arousal system. The discovery, from animal and human studies, that orexin deficiency results in narcolepsy suggested that this system is particularly important in the maintenance of wakefulness. One of the major outputs of the orexinergic system that promotes wakefulness is the direct activation of histaminergic neurons in the tuberomammillary nucleus. Eating behaviour is regulated by a complex interplay of peripheral endocrine stimuli and central neurotransmitter systems, by circadian rhythms and by environmental cues. In this intricate puzzle, both orexigenic and anorexigenic effects of endogenous molecules seem to necessitate the integrity of the histaminergic system (Passani

et al., 2011). Several peptides that function as satiety or hunger signaling molecules, such as orexin, leptin, glucagon-like peptide 1, and thyrotropin-releasing hormone, act through the histaminergic system.

Histamine presumably acts in concert with and complementary to reward systems and learning circuits to influence appetitive behaviours. The appetitive and ingestive phases of feeding behaviour involve very different brain and behavioural mechanisms. Appetite requires a sympathetic response with a high arousal state, and the histaminergic system is crucial to sustain a high degree of arousal during motivated behaviours such as food searching.

Another neuroendocrine interaction that may be important is the effect of orexins on stress hormone secretion and in the hypothalamic-pituitary-axis. Several lines of evidence support a role of the orexins as modulators of the stress response (Winsky-Sommerer *et al.,* 2004).

High-arousal states, including stress, are associated with elevated orexin neurotransmission (Espana *et al.,* 2003) and acute stress increases levels of orexin mRNA (Reyes *et al.,* 2003). Central administration of orexin in rats results in increased plasma adrenocorticotrophic hormone and corticotropin-releasing factor. One of the limbic inputs to orexin neurons might be CRF neurons in the amygdale (Winsky-Sommerer *et al.,* 2004). Excessive activation of orexin neurons during rest period by the limbic input might contribute to sleep disruption under stressful conditions.

Energy homeostasis and appetite regulation are other crucial domains in which the role of the orexin system is of relevance. Orexin itself acts as a weak-to-moderate appetite stimulator, but it also interacts with other neuropeptides/hormones to modulate appetite, namely neuropeptide Y, leptin and ghrelin (Ganjavi and Shapiro, 2007).

Thus, the orexin and histaminergic systems are at the heart of different homeostatic functions, illustrating the intricate relationship between wakefulness, stress reactivity and feeding. Histamine and orexin neurons exert different, but complementary, control on wakefulness, the former being more important for aspects of consciousness and cognitive functions, whereas the peptidergic neurons are involved primarily in behavioural arousal including muscle tone, locomotion and emotional reactions.

9.5.2. Psychological mechanisms

Sleep and eating problems are multifactorial phenotypes, with a bio-psycho-social determination. The transdiagnostic approach to psychopathology is proposed as a important first step toward learning about shared and unique psychological processes in psychopathology. Following this approach to eating and sleep disturbances, we can consider psychophysiological arousal as a common process (Figure 9.1).

Academic and emotional stress is common in college students and stress and psychological distress are two robust contributors to elevated arousal states.
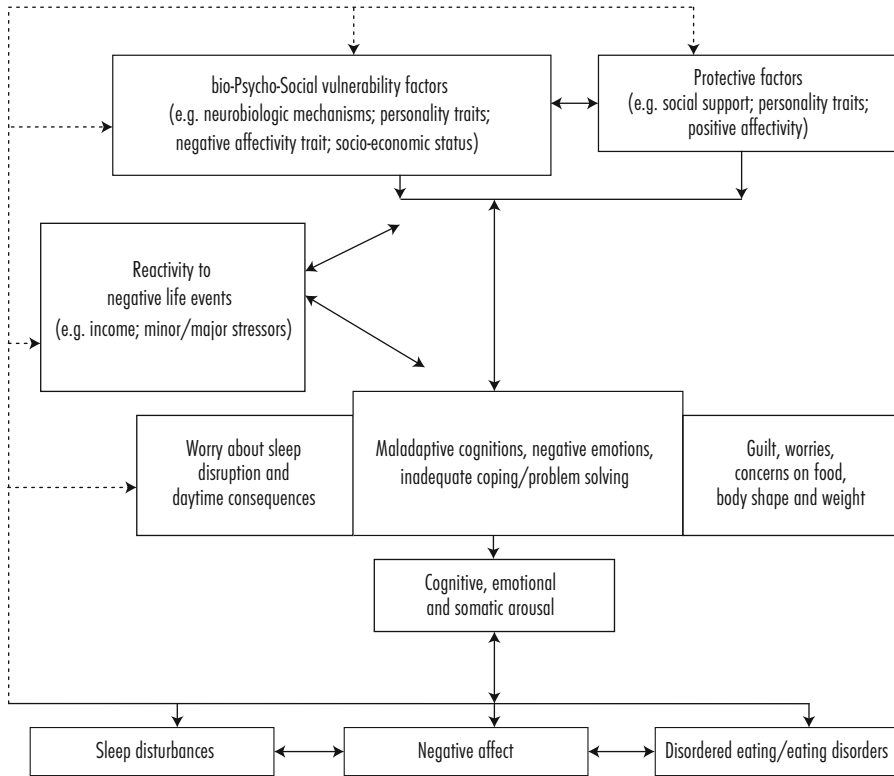
Figure 9.1. Possible bio-psycho-social factors related to both disordered eating and sleep difficulties. Solid lines = possible direct relations; dotted lines = possible retroactive relations.

Difficulties of dealing with stress, maladaptive coping mechanisms (Morin *et al.,* 2003), inadequate cognitive styles, negative emotions/affect (e.g. anxiety, tension, anger, feeling depressed), and some personality traits may increase the impact of stress, contributing to heightened psychophysiological arousal (Azevedo *et al.,* 2010b; Morin *et al.,* 2003). Research showed that psychophysiological arousal completely mediated the association between stress and sleep disruption (Morin *et al.,* 2003). Moreover, stress and negative psychophysiological states may interfere with efforts to maintain diet (Stice and Shaw, 2002) and lead to great food consumption, preferences for sweet/fat food (Adam and Epel, 2007), emotional eating, loss of control over eating and binge eating episodes (Stice and Shaw, 2002). Therefore these eating behaviours are considered a temporary way to cope with stressful life events and to diminish or neutralise negative emotions (Stice and Shaw, 2002). In turn, the occurrence of binge-eating episodes are associated with feelings of failure, concerns about one's ability to control eating and weight and these perpetuate the negative self-evaluation and the need for a restrictive diet.

Among personality traits/temperament characteristics that may predispose people to psychophysiological arousal, the possible transdiagnostic candidates are perfectionism,

neuroticism, impulsivity and harm avoidance. They can increase the impact of stressful life events, and may predispose the individual to higher levels of stress and to psychological distress, such as eating behaviours (e.g. bulimic behaviours) and sleep disturbances (e.g. initial insomnia).

Perfectionism (Wirtz *et al.,* 2007) and the ruminative cognitive style (Zoccola *et al.,* 2008) are associated to increased hypothalamic-pituitary-adrenal axis activation and increased cortisol reactivity to stressful situations, that indicate they have a important role in stress response.

The perfectionism core characteristics are setting of high standards and striving for perfection in association with a morbid fear of failure and a dysfunctional self-evaluation scheme (e.g. self-criticism). Self-critical perfectionism is associated with maladaptive cognitions (e.g. rumination), high sensitivity to criticism, negative affect, maladaptive coping mechanisms (distraction; emotion-oriented coping strategies), that make perfectionists more vulnerable to stress and to psychological distress (Blankstein and Dunkley, 2002), such as sleep difficulties (Azevedo *et al.,* 2010a) and eating behaviours disturbances (Macedo *et al.,* 2007; Soares *et al.,* 2009). The only study exploring the perfectionism contribution to eating and sleep difficulties interrelationship indicated that perfectionism predicted and partially mediated this association (Bos *et al.,* unpublished data).

The personality trait neuroticism is associated with negative coping mechanisms (Watson and Hubbard, 1996), negative affect/emotionality, worry/rumination at night (Quintal *et al.,* 2011), and with increased pre-sleep psychophysiological arousal (Azevedo *et al.,* 2010b). Neuroticism is a risk factor for ED and is associated with poor sleep quality and quantity (Danielson *et al.,* 2010; Gau, 2000; Maia *et al.,* 2008; Quintal *et al.,* 2011), with later sleeping time on school days and with difficulties of waking up in the morning (Gau, 2000). Although, other studies did not replicate these findings and showed that extroversion was positively associated with going to bed late (Maia *et al.,* 2008), these phase delay of sleep seems to be associated with eating disturbances. Therefore, BN patients fall asleep and wake up in the morning about one hour later than healthy controls (Latzer *et al.,* 1999), night eating are associated with ED (Tzischinsky and Latzer, 2004), and a evening circadian preference was related to eating disturbances in adolescents (Schmidt and Randler*.,* 2010).

The personality trait impulsivity contributes to cognitive arousal maintenance (Schmidt *et al.,* 2010), is a common trait of bulimic patients such as AN-B/P; BN and is associated with insomnia severity. Impulsivity interferes with sleep by its association with dysfunctional thought control strategies to an unwanted mental activity at bedtime (e.g. worry) and to the incapacity to inhibit daytime rumination and worries about consequences of insufficient sleep (Schmidt *et al.,* 2010).

The harm avoidance is a temperament feature of ED patients and is higher in insomniacs than in normal controls. Its dimensions anticipatory worry and fatigability are positively associated with sleep latency in insomniacs. Anticipatory worry is also associated with REM latency, and fatigability is associated with REM sleep duration (De Saint Hilaire *et al.,* 2005).

The university students may also experience sleep and eating problems due to their co-morbidity with depression or anxiety disorders, which are probably the most common psychiatric conditions among students population. However, it cannot be excluded that eating and sleep difficulties may intensify or predict personality trait tendencies (Danielson *et al.,* 2010) and anxious and depressive symptoms. Although these common transdiagnostic psychological variables seems to have a important contribution to sleep and eating disturbances explanation, more research is required to explore their contribution to eating/sleep problems interrelationship.

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Summary points

- Skeletal health is achieved through complex and interacting processes that are synchronised hierarchically and in feed-back mechanisms.
- The main regulating hormones involved in mineral metabolism are parathyroid hormone, calcitonin and vitamin D-hormone.
- Bone turnover proceeds in a circadian manner with a peak at night and a trough during the day.
- Within one 24 hr-cycle of turnover, bone resorption displays an amplitude multiple larger than bone formation.
- Intake of food and calcium in particular suppress bone resorption.
- Melatonin is a mediator of bone turnover but its role is not yet well understood.
- A clinical study was administered to clarify whether a dietary supplement taken at night suppresses mainly nocturnal bone resorption.
- There is dietary potential to take advantage of a well-timed dietary intervention with respect to bone health.

10. Sleeptime diet and bone health

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Abstract

Osteoporosis is a multifactorial bone disease with loss of bone mineral and structure, which is predominantly prevalent in aged women after menopause. Due to increasing life expectancy, osteoporosis is becoming more and more important. It should be aimed to develop preventive strategies against bone loss, which are feasible, cost-effective and well-accepted by the public. Bone turnover is orchestrated by a sophisticated hormonal interplay with parathyroid hormone, calcitonin and vitamin D as their main regulators. Other mediators are melatonin and GLP-2. Bone turnover underlies a circadian rhythm which is partly mediated by the cyclical intakes of meals or nutrients, calcium in particular. Calcium is a substrate in bone formation but also a regulator of many biological processes. In general long-term compliance with consumption of foods is higher than with taking tablets. Nevertheless, habitual diets contain too little calcium. Dietary strategies against this deficit involve the advice to increase the consumption of calcium rich or calcium fortified foods, or of diets or foods that contain enhancers of calcium absorption. Beyond that a time-targeted consumption of a 'bone drink or snack' that fulfils these prerequisites, may maximize the bone sparing effect. We have tested this hypothesis in a clinical study with postmenopausal women who consumed a calcium-rich functional milk at bedtime. We have observed a stimulation of calcium utilisation and a reduction of nocturnal bone resorption by this time-targeted approach of dietary intervention.

Keywords: osteoporosis, mineral metabolism, calciotropic hormones, melatonin, functional milk

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Abbreviations

1,25(OH)2D3	1,25-dihydroxyvitamin D, vitamin D-hormone, calcitriol
BAP	Bone alkaline phosphatase
BMD	Bone mineral density
CPP	Casein phosphopeptide
Crea	Creatinin
CTx	C-telopeptide fragments of type 1 collagen degradation
CYP	Cytochrome P
DPD	Desoxypyridinolin-crosslinks
FOS	Fructooligosaccharide
GLP-2	Glucagon-like peptide 2
IGF-1	Insulin-like growth factor 1
MBP	Milk basic protein
NTx	N-telopeptide fragments of type 1 collagen degradation
OPG	Osteoprotegerin
PTH	Parathyroid hormone
RANKL	Receptor activator for nuclear factor kappaB ligand
SCN	Suprachiasmatic nucleus

10.1 Introduction

Bone is a life tissue that is renewed continuously during defined time cycles and within so-called basic multicellular units. The bone degrading process performed by specialised cells (osteoclasts) is coupled with the generation of new bone by the activity of osteoblasts. In bone disease this process gets uncoupled. Bone turnover is a dynamic remodelling process and closely related to mineral metabolism. Bone turnover underlies hormonal regulation and shows circadian rhythm, as will be explained below. Central organs in this context are the pituitary gland where PTH is produced, and the kidney, one target organ of PTH, where it stimulates the synthesis of vitamin D hormone, another key regulator of bone and mineral metabolism. Similar to bone the kidney shows a circadian rhythm. Melatonin is a neuro-hormone secreted by the pineal gland. Also called night-hormone, melatonin is involved in the entrainment of the daily light-dark cycle and is in conjunction with sleep. Melatonin has been found in bone, too, and it is known to affect bone metabolism. Melatonin also occurs in milk.

Bone turnover can be actively affected and altered by external factors including nutrition. Thus the targeted consumption of foods or application of supplements in order to preserve bone health is a matter of public interest. It is uncertain whether a nocturnal dietary intervention with calcium could be advantageous over other timings. More than just delivering the mineral, the targeted impact on hormonal regulation and its circadian course might be a potential to attenuate the increased nocturnal bone resorption. This hypothesis was tested in an intervention study with postmenopausal women.

10.2 Background

10.2.1 Hormonal regulation of bone metabolism

Bone and mineral metabolism are steered by a diversity of subtle endocrine processes that are involved in maintaining calcium homeostasis and in erecting and degrading bone tissue. Physiologically, osteoclastic resorption of old or injured bone and the formation of new bone by osteoblasts are kept in a tightly coupled balance (Eriksen, 2010). These processes are predominantly steered by a complex and interacting hormonal regulation with PTH, calcitonin and vitamin D-hormone (1,25-dihydroxyvitamin D or 1,25[(OH)2D3]) as their key regulators.

PTH has both catabolic and anabolic effects on bone (Silva *et al.*, 2011). Plasma PTH is known to be negatively associated with BMD, but obviously not in all ethnic groups (Yan *et al.*, 2003), pointing to a genetic component in the susceptibility to PTH-dependent regulation of BMD. PTH regulates the synthesis of vitamin D-hormone in the kidney where it stimulates the expression of the CYP27B1 gene, which encodes the synthesis of 1α-hydroxylase in the proximal tubule cell. This process is more effective in the young and declines with age irrespective of a stimulated CYP27B1 gene expression (Armbrecht *et al.*, 2007). In the absence of PTH, levels of cellular 1α-hydroxylase, the key enzyme to convert 25(OH)D3 into 1,25(OH)2D3, decrease (Murayama *et al.*, 1999).

Calcitonin plays an important role in the maintenance of serum 1,25(OH)2D3 under normocalcemic conditions (Zhong *et al.*, 2009). In response to low plasma calcium levels, 1,25(OH)2D3 stimulates PTH secretion from the parathyroid gland. High plasma calcium concentrations or elevated 1,25(OH)2D3 levels signal the decrease of PTH synthesis in a negative feed-back regulation by suppression of PTH transcription rate (Landry *et al.*, 2011; Naveh-Many and Silver, 1990).

1,25(OH)2D3 stimulates the active intestinal calcium absorption by enhancing gene expression of calcium transporters and binding proteins in the enterocyte, while oestrogen and IGF-1 enhance calcium absorption independent of vitamin D signalling (Fleet and Schoch, 2010). The postmenopausal state is one risk factor among others for osteoporosis because it induces lower calcium absorption as a consequence of a shortage of oestrogen and IGF-1 (Fanciulli *et al.*, 2009). Like other steroid hormones, 1,25(OH)2D3 provides negative feedback of its own production by inhibiting hydroxylation of its precursor in the kidney. Receptors for 1,25(OH)2D3 are located in the distal nephron that enable the regulation of renal calcium reabsorption. Like 1,25(OH)2D3, PTH binds to specific receptors in the kidney and signals to increase calcium reabsorption and decrease phosphate reabsorption. Evidently, the kidney plays a major role in the homeostasis of calcium and bone metabolism.

10.2.2 Circadian rhythms of the kidney

The kidney is an organ that exhibits a circadian rhythm of physiological processes and functions in response to the master pacemaker of the circadian clock, which is located in the SCN of the brain. This pacemaker is entrained by light signals transmitted from the retina through the retinohypothalamic tract and successively activates a series of genes that form an auto-regulatory feed-back loop with one cycle taking about 24 hrs. The SCN synchronises the functions of peripheral clocks of organs (Albrecht, 2006; Stow and Gumz, 2011). The molecular evidence for a circadian rhythm of kidney function has been identified in the expression of clock-controlled genes in this organ. The production of urine volume is higher during the day than at night, reflecting the circadian oscillation of renal blood flow and glomerular filtration rate. Accordingly show urinary excretion of sodium, potassium, phosphorous, magnesium, acid, and chloride circadian changes (Stow and Gumz, 2011).

The SCN is hardly perturbed by dietary pattern, in contrast to peripheral clocks like in the liver, which are entrained by feeding cycles (Vollmers *et al.*, 2009). Food intake and time of feeding has profound effect on rhythmic gene expression independent of the core oscillator genes. Conversely, a smaller set of core clock genes at the organ level is expressed in the absence of rhythmic pacemakers like day/light cycle or mealtime feeding (Vollmers *et al.*, 2009). So far it remains unclear how the hierarchies between the different levels of clock regulation and their interaction are established. Understanding this interplay is the prerequisite to influence bone turnover and resorption, and to develop tools for osteoporosis prevention.

10.2.3 Circadian rhythms of bone

A circadian rhythm has been described for bone metabolism with activity peaks during the late night, a decline in the morning and troughs during the day (Nielsen *et al.*, 1990, 1991; Nielsen, 1994), as indicated by the variations of bone resorption markers, like CTx or NTx in serum or urine, and for markers of bone formation, like osteocalcin or BAP, but to a much smaller extent (Figure 10.1).

Like BAP, osteocalcin varies diurnally with activity peaks during the night and a decline in the morning. This process is apparently not related to sleep (Gundberg *et al.*, 1985; Nielsen *et al.*, 1990, 1991) but regulated by endogenous cortisol (Nielsen, 1994). Sleep deprivation itself was associated with lower cortical bone density (Specker *et al.*, 2007), and practicing napping with higher BMD (Nakagi *et al.*, 2010).

Procollagen type 1 carboxyl-terminal propeptide, a marker of bone formation was observed to oscillate in a circadian manner as well (Pedersen *et al.*, 1995). OPG is a cytokine of osteoblastic origin that displays a circasemidian rhythm (Tarquini *et al.*, 2005). Together with the receptor activator for nuclear factor kappaB ligand, OPG is a key regulator of osteoclastogenesis in that it shifts bone metabolism towards bone formation over bone resorption (Lacey *et al.*, 1998). In animal experiments and cell culture studies it was shown that PTH (1-38) peptide or intact
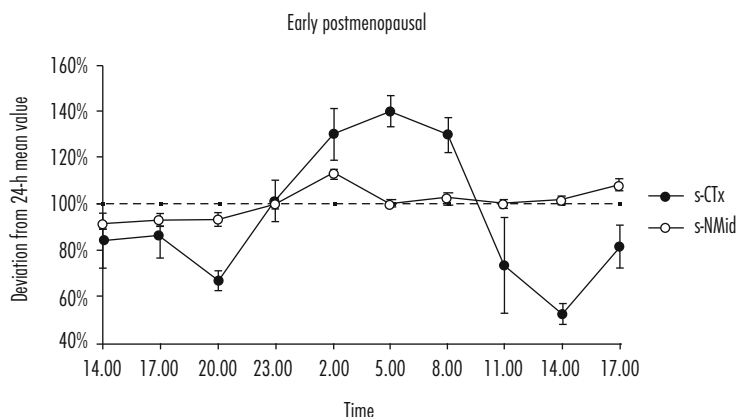
Figure 10.1. Diurnal variation of markers of bone resorption (s-CTx: carboxyterminal telopeptide region of the type 1 collagen) and formation (s-NMid: osteocalcin) in early postmenopausal women. Both markers (mean and SEM) varied cyclically and significantly, but much more distinct in case of s-CTx (reprinted from Qvist *et al.*, 2002, with permission from Elsevier).

PTH decreased OPG mRNA expression and stimulated RANKL (Huang *et al.*, 2004), thereby triggering a state of bone resorption over formation.

To what extent circadian variation of bone turnover is responsive to meals or other variables, or whether bone resorption is truly circadian is not entirely clear. Fasting reduced the variation of bone resorption markers, while intake of food or single nutrients like glucose, fat, and protein reduced the amplitude of bone resorption, as indicated by CTx (Bjarnason *et al.*, 2002; Qvist *et al.*, 2002). The intravenous infusion of calcium decreased the nocturnal urinary NTx peak to some extent in young and postmenopausal women, but the decline (7.5±1.9 compared with 4.1±1.5 nmol/mmol crea) was significantly greater when the baseline values were higher (baseline mean±SEM; 25.7±2.1 nmol/mmol crea), like in postmenopausal women compared with young women (baseline mean±SEM 19.3±1.7 nmol/mmol crea) (Ledger *et al.*, 1995). When energy supply was restricted, bone formation was disturbed first and more markedly than bone resorption, which started to increase not before a certain level of energy restriction was achieved. Bone resorption became uncoupled from formation and coincided with oestradiol suppression (Ihle and Loucks, 2004).

It has been shown that physical activity, gender, age, menopause, endogenous cortisol production, blindness and fasting play a role in setting the absolute level of bone turnover, but do not affect the circadian character of bone resorption (Qvist *et al.*, 2002; Schlemmer and Hassager, 1999). Bone markers indicate a clearly lower circadian rhythm of bone formation than bone resorption which decreased acutely after feeding. This process might be mediated by calciotropic hormones which respond to certain nutrients like calcium or phosphorus. At least part of the night-time

peak of bone resorption reflects feeding/fasting rhythm. After all it seems more promising to target bone resorption than formation.

The bone resorption marker DPD increased at night in healthy women and in osteoporotic women at a higher degree, indicating that a more profound rise of nocturnal bone demineralisation goes along with this skeletal disorder. Serum ionised calcium level did not change in both groups. Urinary excretion of calcium decreased at night in normal women but remained unchanged in osteoporotic women, showing a lack of capacity to counterbalance the nocturnal rise of bone resorption (Eastell *et al.*, 1992).

The nocturnal increase of bone resorption coincided with the lowest circulating levels of GLP-2, a gastrointestinal hormone with pleiotropic intestinal functions including growth and mobility, blood flow, digestion and absorption (Dubé and Brubaker, 2007). When GLP-2 was injected subcutaneously a significant and acute reduction of bone resorption was observed. Accordingly, part of the circadian variation of bone resorption might result from the meal or nutrient-induced variation of GLP-2 release during the 24 hr cycle (Henriksen *et al.*, 2004).

Initially, the main outcome of studies on circadian variation of bone resorption was to realize the necessity for constant and standardized samplings of blood and urine for marker analysis. From the clinical viewpoint, there was tremendous improvement with the development of more specific bone resorption markers like DPD, CTx and NTx replacing urinary hydroxyproline, a previously often used bone resorption marker. DPD is not forged by meals and diet, in contrast to hydroxyproline. Hydroxyproline reflects collagen breakdown during bone resorption but is also adulterated by collagen from meals, and therefore is not a specific bone resorption marker. Later on awareness arose on the potential for a time-targeted use of supplements, meals, (functional) foods, nutrients or additives in order to smoothen the peaks of bone resorption stimulators like PTH. The ingestion of signalling peptides to mimic the effect of feeding (Walsh and Henriksen, 2010) appears to be a further mean to steer bone turnover.

10.2.4 Circadian rhythms of parameters of mineral metabolism

Circadian rhythms have been reported for ionized calcium, total calcium and phosphate, but with different shapes. These differences presumably reflect a combination of the distinct metabolic routes and functions. Ionized calcium showed a U-shaped curve with a peak at 11:00 and a trough at 15:30, while total calcium displayed a W-shaped curve with maxima at 01:00 and 11:00 and troughs at 05:00 and 18:00. Phosphate showed an M-shaped curve with peaks at 3:30 and 16:00 (Markowitz *et al.*, 1984).

PTH, one of the main modulators of mineral and bone metabolism showed a profound circadian rhythm. PTH oscillated in a specific pattern with a peak at night and in the afternoon and a nadir in the morning (Calvo *et al.*, 1991; Nielsen *et al.*, 1991). No perturbance of this nocturnal rhythm by sleep depriviation was observed (Nielsen *et al.*, 1991). When subjects performed their main sleep at daytime, a diurnal rhythm was still present but less distinct than during the main

sleeptime being at night. Obviously, PTH rhythm was affected by sleep in general (Chapotot *et al.*, 1996).

In another experiment the bimodal or circasemidian rhythm of PTH was confirmed when the subjects were under their baseline conditions with usual periodic day-night activity. A primary peak was seen at about 03:00 h, and a secondary peak at 17:00 h, and a primary and secondary nadir at about 11:00 and 21:00 hrs (El-Hajj Fuleihan *et al.*, 1997). When the women were at constant environmental conditions with respect to meals, diet, posture, or sleepwake-related events, a circadian rhythm was still observed. However, the characteristics of the curve had changed from a circasemidian to a circadian rhythm with a blunted nocturnal PTH peak (Figure 10.2).

The bimodal rhythm of PTH was confirmed for healthy elderly men and premenopausal women but interestingly not for postmenopausal women. These were characterized by one sustained increase in PTH concentration during night-time (Joseph *et al.*, 2007). Accordingly, PTH rhythm has a truly endogenous component and, in addition, is shaped by exogenous or environmental events including meal or oestrogen deficit. In some abnormalities like primary hyperparathyroidism (Lobaugh *et al.*, 1989) or growth hormone deficiency (Ahmad *et al.*, 2003) PTH circadian rhythm is obviously absent.

10.2.5 Modulation of parathyroid hormone

Plasma calcium is one regulator of PTH levels. The suppression of PTH in response to a calcium infusion (Ledger *et al.*, 1995) or supplement (Fardellone *et al.*, 1998) was observed when the habitual intake of calcium was below recommendation (800 mg/d) whereas no PTH response was seen at dietary calcium intakes above that value (800-1,600 mg/d), (Fardellone *et al.*, 1998). These findings imply a threshold value of dietary calcium above which an additional calcium intake has no further effect on PTH and thus PTH-mediated bone resorption.
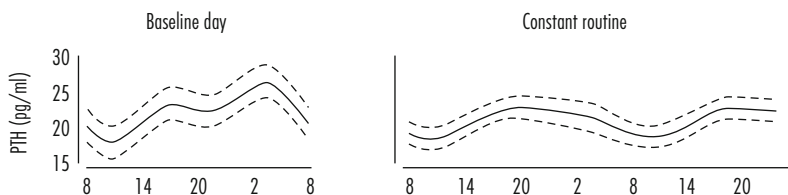
Figure 10.2. Diurnal variations of plasma parathyroid hormone (PTH) at different environmental factors. The estimated population mean rhythm curves (±2 SD) for plasma PTH on the baseline day (left) and during the constant routine with respect to diet, meal, posture, or sleepwake-related events (right). Note that the observation time is more expanded during the constant routine (El-Hajj Fuleihan *et al.*, 1997).

In a set of three short-term studies over 24 hrs Kärkkäinen *et al.* (2001) investigated the effects on bone metabolism of: (a) the timing of a single dose of 25 mg/kg body weight calcium supplements, either in the morning or at night; (b) the size of a single dose (250 vs. 1000 mg); and (c) the portioning of the dose in healthy young women (4 times 200 mg every four hrs).

In the timing-experiment (a) serum ionised calcium concentrations increased after the calcium load, remained high for 4-6 hrs with values returning to baseline after 10 hrs. The timing of supplementation had no effect. PTH decreased within 1 hr after the calcium loads, with a steeper trough after the morning compared with the sleeptime dose, but a quicker return to baseline. The total postload urinary excretion of calcium did not differ between the day- or night-load of calcium.

The higher calcium dose in study (b) initiated higher plasma levels of ionised calcium and lower levels of PTH within 2-6 hrs postprandially, with values approaching baseline thereafter. The postload urinary excretion of calcium increased and was higher after a load of 1000 mg compared to one of 250 mg, indicating that the rise in urinary calcium after a supplement reflects an increase in calcium absorption.

The advantage of dividing a large single dose into four distributed over the day like in study (c) lies in prolonged lower levels of PTH at prolonged higher levels of serum ionised calcium. However, the diurnal rhythm of PTH with low values at day and high values at night was maintained after portioning the dose and irrespective of the repetitive calcium supplementation, albeit at lower concentrations. No effect was observed in any of the bone markers, which might not be surprising because of the single-meal character of the experiment. Under this condition the observation time was too short to detect changes in bone resorption.

10.2.6 Melatonin and bone

Melatonin is an indolamin and a neurohormone produced by the pineal gland from the precursor tryptophan via serotonin. It is involved in the entrainment of the daily light-dark cycle and is conjuncted with sleep. Melatonin has also been found in the gastrointestinal tract and in high concentrations in bone marrow, an observation that illustrates its role in bone metabolism and function, probably through its antioxidative properties. Melatonin obviously mediates bone sparing effects which may be one explanation for the observed association of higher BMD in subjects that practiced napping (Nakagi *et al.*, 2010).

Osteoblasts express melatonin receptors, with lower levels in older age (Sánchez-Barceló *et al.*, 2011). Melatonin stimulated osteoblast differentiation and activity, with a higher BAP expression and an arrestive effect on osteoclast differentiation in cell culture (Garcia-Parrilla *et al.*, 2009). In bone cells of a mouse model melatonin decreased the expression of RANK mRNA, a cytokine that stimulates bone resorption, and increases the expression of osteoprotegerin, a protein that inhibits the differentiation of osteoclasts.

In animal models the role of dietary melatonin on bone is less clear (Garcia-Parrilla *et al.*, 2009). In ovariectomized rats, a model for postmenopausal osteoporosis, trabecular thickness, trabecular area and bone mineral decreases following experimentally induced oestrogen deficiency (Scholz-Ahrens *et al.*, 2002; Uslu *et al.*, 2007). The administration of melatonin to this animal model prevented the loss of trabecular and cortical bone at some sites but did not prevent loss of BMD (Uslu *et al.*, 2007). More information is needed on the mosaic of the role of melatonin in bone health.

Melatonin is also synthesised in plants where it is involved in steering the light/dark cycle-depending photosynthesis. Some plant foods are rich in melatonin and could serve as natural sources of this bioactive compound. They also have the potential to be utilized as base product for functional foods (Garcia-Parrilla *et al.*, 2009). The melatonin contents of carrot or apple are about 50 pg/g wet weight. Very high values were found in purslane (Simopoulos *et al.*, 2005). Melatonin is naturally occurring in milk at concentrations about 5-25 pg/l, with values higher in night milk than day milk (Jouan *et al.*, 2006). The intake of food or of certain nutrients, or of tryptophan-rich proteins can serve as stimuli for melatonin release.

10.3 Sleeptime dietary intervention and bone metabolism

Whether circulating PTH displays anabolic or catabolic effects depends on its plasma concentration and the time of observation. The manipulation of the PTH rhythm is a promising tool to prevent or treat bone diseases by affecting nocturnally increased bone turnover (Fraser *et al.*, 2004). The support of primary prevention of bone loss by dietary means has turned out to be an interesting challenge for physiologists, nutritionists, food technologists and physicians.

We investigated the effects of milk supplements taken at bedtime on characteristics of bone metabolism in 85 healthy postmenopausal women (Adolphi *et al.*, 2009). Milk is a calcium-rich food that also contains many other nutrients critical for bone, like magnesium, potassium, phosphorus, zinc, vitamins K, B12, and folic acid. Supplementation with milk has been shown to significantly attenuate postmenopausal loss of bone mineral density in a long-term study with Chinese women (Chee *et al.*, 2003). The experimental design was based on findings in the literature (Blumsohn *et al.*, 1994) of a circadian rhythm of bone metabolism and of observations showing that main regulators of bone resorption and mineral metabolism can be modulated by dietary intervention. The night-timing promised to maximize the debilitating effect on nocturnal bone resorption. In this context urine samples were separated in day- and night fractions. The hypothesis was that: (1) bedtime consumption of fermented milk inhibits the nocturnally increased bone resorption optimally; (2) this effect is more pronounced when the milk was supplemented with calcium; and (3) inhibition of bone resorption is most effective when calcium absorption enhancers were added beyond.

After two weeks of intervention urinary excretion of calcium and phosphorus was significantly higher than baseline values in the night-urine fraction (231±14 vs. 184±14 mg Ca/g crea; $P<0.05$

and 1,104±28 vs. 994±28 mg *P*/g crea; *P*<0.01), indicating that more calcium had been absorbed. In the day-urine fraction this difference was not significant (202±10 vs. 188±10 mg/g Ca/crea; ns and 913±27 vs. 907±27 mg *P*/g crea; ns).

Total plasma calcium decreased but ionized calcium remained unchanged after supplementation. The lower plasma total calcium might reflect the reduction of bone turnover as a secondary effect to slightly lower plasma PTH concentrations (41.2±11.7 ng/l) after two weeks of intervention compared to baseline values (47.9±11.7 ng/l). The increase of plasma phosphorus after calcium supplementation is in line with observations by Kärkkäinen *et al.* (2001). The significantly lower values of plasma BAP as a marker of bone formation, and of DPD as a marker of bone resorption indicated a decrease of bone turnover and hence a bone mineral sparing effect following the milk drink at bedtime (Figure 10.3).

This effect could have been mediated by additional calcium, originary occurring milk melatonin, supply of the melatonin precursor tryptophan with milk protein, supply of originary occurring bioactive milk peptides known to improve bone mineral like CPP and MBP. MBP has been proven to diminish the loss of bone mineral in postmenopausal women (Aoe *et al.*, 2005).

In a further step, the subjects were stratified according to the three experimental dietary groups: A; fermented milk, B; fermented milk enriched with milk minerals, or C; fermented milk enriched with milk minerals plus the absorption enhancers CPP and FOS, a combination of long-chain and short-chain inulin-type fructans. CPP and FOS have been shown to improve calcium absorption and bone mineral content at certain conditions (Scholz-Ahrens and Schrezenmeir, 2000; Scholz-Ahrens *et al.*, 2007). Significantly higher concentrations of phosphorus (Figure 10.4a) and calcium (Figure 10.4b) in the night urine were observed in the milk group supplemented with milk minerals plus absorption enhancers C compared with B. Contrary to expectation, the largest decrease of bone resorption occurred in the reference group A, as indicated by DPD, with no significant differences between groups (Figure 10.4c).
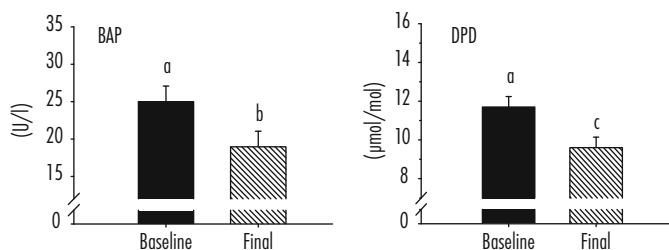
Figure 10.3. Baseline and final concentrations of markers of bone formation (BAP) and bone resorption (DPD) in the night urine fraction of postmenopausal women (mean and SEM). The women consumed 175 ml of a fermented milk at bedtime irrespective of the supplement (n=85) (Adolphi *et al.,* 2009: Figure 2. With kind permission from Springer Science+Business Media).
a,b: *P*<0.05; a,c: *P*<0.01. In the day urine fraction no difference was seen.
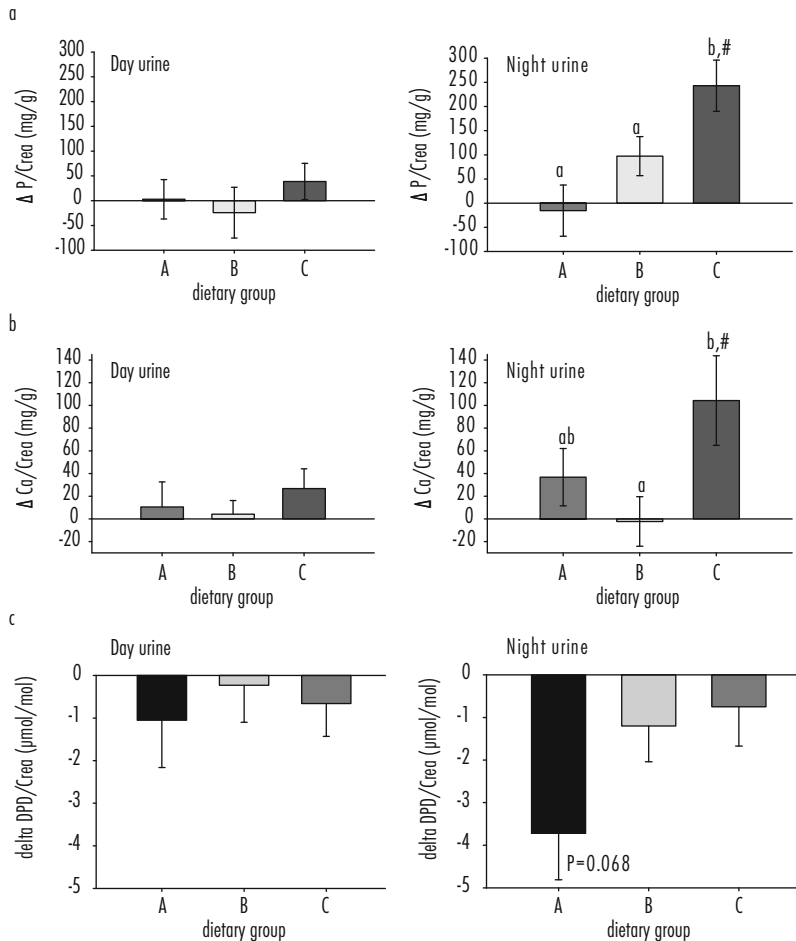
Figure 10.4. Different effects of functional milks on urinary excretion of phosphorus (a), calcium (b) and bone resorption marker desoxypyridinolin-crosslinks (DPD) (c) in the day or night urine fraction. Changes are mean ± SEM (baseline minus final concentrations) after two weeks intervention with one cup of 175 ml of a fat-reduced functional milk.

A. fermented milk, containing 210 mg calcium and 160 mg phosphorus per cup (reference group, n=28), B. fermented milk + milk minerals from a calcium-rich mineral fraction providing additional 510 mg calcium and 320 mg phosphorus per cup, n=29, and C. fermented milk + milk minerals + 0.175 g/cup casein phosphopeptide (CPP) and 1.75 g/cup fructooligosaccharide (FOS) (modified after Adolphi *et al.*, 2009: Table 2 and Figure 1. With kind permission from Springer Science+Business Media).

Groups not sharing a common letter are significantly different. #: significantly different from baseline.

The decline of PTH was not significant after the bedtime consumption of a milk supplement, and there was no difference between the functional milks (Adolphi *et al.*, 2009). The discrepant finding to that by Kärkkäinen *et al.* (2001) could be explained by the timing of sampling. After more than 10 hrs fast values obviously had almost returned to baseline the next morning, as they did in the study by Kärkkäinen *et al.* (2001), who also reported a decrease of PTH in response to calcium ingestion within 2-4 hrs but no longer thereafter up to 10 hrs. However, the enhanced bone resorption usually observed during the fast at night was alleviated, even at just slightly reduced PTH levels. We did not test whether our observations would have been different if supplementation had occurred in the morning or during the day. However it was quite obvious that these main effects would have been overlooked in a pooled 24-hr urine sample. The data support the view of a dietary potential to reduce nocturnal bone resorption.

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Metabolism, metabolic syndrome, obesity and sleep

Summary points

- The peptide ghrelin is produced mainly by the stomach and acts as an endogenous ligand for the growth hormone secretagogue receptor.
- The biological functions of ghrelin include growth hormone release, appetite-stimulatory effects, regulation of energy homeostasis and gastrointestinal motility as well as modulation of higher brain functions (memory, mood, reward-associated behavior, sleep).
- Sleep deprivation (sleep restriction) increases circulating ghrelin concentrations.
- Increased ghrelin concentrations induce feelings of hunger as well as a positive energy balance.
- The peptide ghrelin links sleep and metabolism.

11. Ghrelin: a gastric peptide linking sleep and energy balance

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Abstract

Ghrelin is a 28-amino-acid-peptide produced mainly by the stomach and acts as endogenous ligand for the growth hormone secretagogue receptor. This chapter gives an overview of ghrelin's biological functions associated with sleep and energy balance. The chapter reviews the secretion of ghrelin and associated phenomena under physiological conditions and in subjects with disrupted sleep-wake patterns. The chapter also discusses studies assessing the effect of experimental ghrelin administration (synthetic growth hormone secretagogue receptor ligands respectively) on sleep and metabolism. Based on today's state of knowledge, ghrelin is one of the key players that link sleep and metabolism. There are reciprocal effects between ghrelin secretion, energy balance and sleep. The underlying mechanisms of this highly complex regulation are a field of extensive biomedical research.

Keywords: growth hormone secretagogue receptor, sleep deprivation, obesity, weight gain

Abbreviations

BMI   Body mass index
CNS   Central nervous system
GHS-R   Growth hormone secretagogue receptor
iRBD   Idiopathic rapid-eye-movement sleep behavior disorder
PD   Parkinson's disease

11.1 Introduction

Ghrelin, a 28-amino-acid-peptide, was discovered by Kojima and colleagues in 1999 as endogenous ligand for the GHS-R (Kojima *et al.*, 1999). Ghrelin is produced mainly by X/A-like cells of the stomach (Date *et al.*, 2000) and is post-translationally modified by acylation of the amino-acid serine at position 3 of the peptide. The resulting peptide is named acylated ghrelin. This post-translational modification by the enzyme ghrelin o-acyltransferase is necessary for ghrelin's biological effects mediated by the GHS-R. Non-acylated ghrelin – the predominant form of circulating ghrelin in blood – is not biologically inactive (as previously thought), but most likely acts by mechanisms and via receptors to be identified. There are also data indicating that acylated and non-acylated ghrelin might have converse effects. Unfortunately, most studies published so far in this field did not differentiate between the acylated and the non-acylated form of ghrelin making the interpretation of the data derived from these studies difficult.

Besides growth hormone release, an appetite-stimulatory effect was one of the first recognized biological functions of ghrelin (Asakawa *et al.*, 2001). Meanwhile, a much broader spectrum of biological functions has been identified including regulation of gastrointestinal motility, energy homeostasis, glucose metabolism as well as modulation of higher brain functions (memory, mood, reward-associated behavior, etc.). Tolle and colleagues were one of the firsts to link ghrelin's function to the regulation of the sleep-wake pattern (2002). In summary, ghrelin promotes sleep, especially slow wave sleep (Kluge *et al.*, 2010, 2008; Weikel *et al.*, 2003), and is one of the key players linking sleep, feeding and energy homeostasis.

11.2 Regulation of ghrelin secretion by eating and sleeping

Under fasting conditions, ghrelin concentrations increase (high pre-prandial concentrations exerting an appetite-stimulating effect), decline postprandially and consecutively slowly recover again over the following hours to initiate new food intake (Carlson *et al.*, 2009; Serra-Prat *et al.*, 2009; Unger *et al.*, 2011) (illustrated in Figure 11.1). Spiegel and colleagues (Spiegel *et al.*, 2011) have investigated the circadian rhythm of ghrelin secretion in healthy subjects. In this study, the postprandial decline and consecutive rebound in ghrelin concentration were independent of the time of day, but were impacted by sleep: during sleep, the recovery of (acylated) ghrelin concentrations was less pronounced and (following an initial acrophase during the first part of
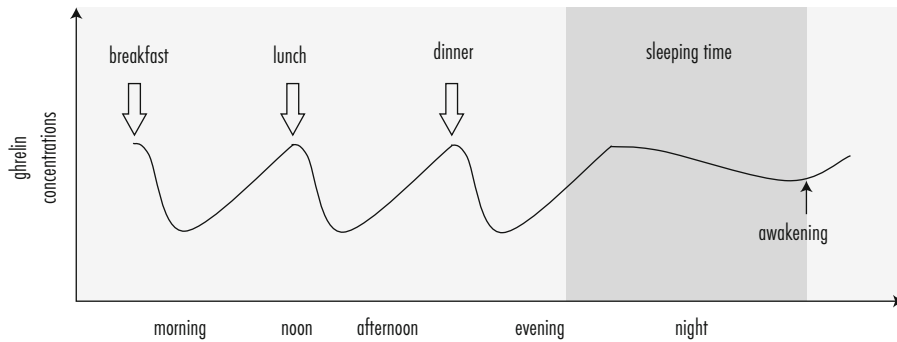
Figure 11.1. Course of ghrelin concentrations in relation to daytime, food intake and sleep (based on Spiegel *et al.*, 2011 and Unger *et al.*, 2011).

sleeping time) ghrelin concentrations spontaneously declined while sleeping until awakening in the morning. This is remarkable, as the subjects were still in a fasting state. Immediately after awakening ghrelin concentrations increased again until the subjects consumed the first meal of the day. These data indicate an inhibitory effect of sleep on ghrelin concentrations, ghrelin secretion respectively. Physiologically thinking, suppression of an orexigenic signal (mediated by ghrelin) during sleep appears reasonable, as feelings of hunger could have sleep-disrupting effects.

While sleep slows down ghrelin secretion (although the subject is in a fasting state), sleep deprivation (Schmid *et al.*, 2008) and sleep restriction (Spiegel *et al.*, 2004) in an experimental setting have been shown to increase ghrelin concentrations (and consecutively also feelings of hunger) in healthy subjects. It is of note that sleep curtailment is not only associated with increased ghrelin concentrations in an experimental short-time setting as shown by the aforementioned studies (Schmid *et al.*, 2008; Spiegel *et al.*, 2004), but relatively high ghrelin concentrations are also seen in subjects with a habitual short sleep time: in a population-based study (n=856) Taheri and colleagues found that sleep duration was negatively associated with ghrelin concentrations (2004), i.e. the shorter the time the subjects usually spent sleeping, the higher the individual ghrelin concentrations. A similar association was found for the BMI in this study: in subjects sleeping less than 8 hrs per night, the BMI was inversely correlated with sleep time. Beside sleep restriction in an experimental short-time setting and a reduced sleep duration as individual (voluntary) habit, preliminary data indicate that long-term externally imposed sleep curtailment in shift workers has a similar impact on ghrelin concentrations (Crispim *et al.*, 2011).

11.3 Impact of ghrelin dysregulation on energy homeostasis

Altered sleep-wake-patterns (reduced sleep time respectively) are associated with increased ghrelin concentrations and weight gain (Patel, 2009, 2008; Patel and Hu, 2008; Patel *et al.*, 2006). Although it remains to be shown that ghrelin is the main factor responsible for weight gain observed in subjects with chronically disrupted sleep, it is likely that ghrelin represents one of the

key players linking sleep and weight gain for several reasons: (a) increased ghrelin concentrations exert an orexigenic effect (that results in increased food intake and consecutively in a positive energy balance); (b) elevated ghrelin concentrations impair glucose tolerance by suppressing the glucose-stimulated insulin secretion (Tong *et al.*, 2010); (c) experimental data suggest that fat mass storage is increased by ghrelin independently of food intake (Perez-Tilve *et al.*, 2011), i.e. independently of ghrelin's orexigenic signal. The authors of the latter study therefore conclude that mechanisms different from hyperphagia contribute to ghrelin-induced weight gain (Perez-Tilve *et al.*, 2011).

11.4 Ghrelin exerts sleep-promoting effects

Copinschi and colleagues have shown that an oral GHS-R agonist (MK-677) improves sleep quality and increases REM (rapid eye movement) sleep in an age-dependent manner (1997). Other studies that investigated the effect of intravenous ghrelin administration in humans also reported sleep-promoting effects but differential effects on distinct sleep stages depending on age and gender (Kluge *et al.*, 2010, 2008; Weikel *et al.*, 2003). In addition, the finding of lower ghrelin concentrations in subjects having problems falling asleep, i.e. in subjects suffering from insomnia (Motivala *et al.*, 2009), support the assumption of sleep-facilitating effects that are mediated by ghrelin. The hypothesis that ghrelin promotes sleep is further endorsed by the finding that ghrelin knock-out mice spend less time sleeping compared with wild type mice. Interestingly, no major impairments in basic regulatory mechanism of sleep and wakefulness are seen in these knock-out mice, arguing for a redundant function of ghrelin in the sleep regulating system (Szentirmai *et al.*, 2007).

As previously described, a moderate increase of ghrelin concentrations occurs physiologically during the first part of the night and is followed by a minor dip in ghrelin concentrations during the second part of the night. This course of ghrelin concentrations indicates that concentrations below a certain threshold (that might be necessary to induce feelings of hunger) promote and sustain sleep. Investigations in subjects with night-eating-syndrome, a disorder characterized by frequent nocturnal awakenings followed by food intake, revealed conflicting results concerning ghrelin concentrations. It therefore remains to be shown whether or not excessive ghrelin secretion during the night might disrupt sleep due to feelings of hunger.

In summary, ghrelin modulates the sleep-regulating system and moderate (physiological) ghrelin concentrations most likely mainly have sleep facilitating effects. The exact effects of ghrelin on sleep depend not only on the concentration of the peptide but also on a number of other factors like age, gender, part of the night, timing between ghrelin peaks and distinct sleep stages, etc.

11.5 Paradoxical low ghrelin concentration in obese subjects

Sleep restriction (either externally imposed or voluntary) stimulates ghrelin secretion that results in feelings of hunger, increased food intake, and consecutively in a positive energy balance and (on the long run) in weight gain. It is therefore surprising that in obese subjects low ghrelin concentrations have been consistently documented (Shiiya *et al.*, 2002; Tschop *et al.*, 2001). This paradoxic finding could be explained by adaptive mechanisms in ghrelin secretion resulting in a decrease of initially elevated ghrelin concentrations in subjects with progressive weight gain. Longitudinal studies, e.g. in subjects starting on shift work, could help to understand the interaction between disruption of the sleep-wake-pattern, alterations in ghrelin concentrations and dynamics in body weight.

11.6 Parkinson's disease: a model for investigating ghrelin secretion and associated phenomena?

In a cross-sectional study we investigated the postprandial ghrelin response after a standardized test-meal in patients with PD, patients with iRBD (a condition considered as a risk factor for subsequent development of PD), and healthy subjects. The postprandial recuperation of ghrelin concentrations in the late postprandial phase was reduced in patients with iRBD and PD compared with healthy controls. In addition, overall ghrelin concentrations were descriptively lower (although not statistically significant due to a very high inter-individual variability of ghrelin concentrations) in iRBD and PD patients compared with the healthy controls (Unger *et al.*, 2011). Since others have shown that ghrelin exerts neuroprotective effects in an animal model of PD (Andrews *et al.*, 2009), we concluded that the reduced ghrelin concentrations seen in our group of iRBD and PD patients might have contributed to the neurodegenerative process underlying PD by increasing the vulnerability of neuronal structures.

Aside from ghrelin's potential role as a modulator of neurodegeneration, PD could represent a model disease for investigating ghrelin secretion and associated phenomena for a number of reasons: a poor sleep efficiency and distinct sleep disorders (e.g. iRBD, excessive daytime sleepiness, sleep attacks, restless legs syndrome) are frequently seen in PD patients, sometimes already in pre-motor stages. Besides sleep disorders, also metabolic alterations (co-morbidity of PD and diabetes mellitus (Schernhammer *et al.*, 2011)), weight changes (mostly weight loss) but also pathological eating habits (e.g. binge eating under dopamine replacement therapy) are observed in a substantial number of PD patients. Given the high inter-individual variability of ghrelin concentrations, it would be compelling to test whether or not individual ghrelin concentrations correlate with (or even predict) markers of sleep and metabolism in this patient group. Given the relatively high incidence of sleep disorders and metabolic changes in PD patients, longitudinal follow-up studies could help to clarify whether or not alterations in sleep profiles and weight (that occur over time) go along with altered ghrelin concentrations. One study reported that in PD patients suffering from weight loss, a low BMI correlated with low ghrelin concentrations (Fiszer

et al., 2010). Yet, there are no studies so far investigating the association between sleep parameters or the presence of sleep disorders and individual ghrelin concentrations in PD patients.

As the spectrum of PD-related non-motor symptoms largely overlaps with ghrelin's biological functions, PD represents an ideal model disease for upcoming investigations of ghrelin's role in the regulation of sleep and metabolism.

11.7 Future challenges and caveats to be considered

The effects of ghrelin on sleep and metabolism are complex and only marginally understood. Studies aiming to reveal ghrelin's role in human sleep and metabolism (but also in other biological systems) have to deal with a number of challenges and also some caveats need to be considered when interpreting the results of these studies:

- Ghrelin regulates basic biological functions that are mutually exclusive: eating and sleeping cannot be performed simultaneously. The biological effects of ghrelin are therefore likely dose-dependent (i.e. there might be different thresholds for ghrelin that generate a response in the respective target system). The sensitivity of certain biological systems to increasing (or declining) ghrelin concentrations might also be modified by the presence or absence of co-factors to be identified.
- Secretion of ghrelin might undergo adaptive processes over time, especially under conditions of dysregulation: while excessive ghrelin concentrations (e.g. caused by sleep deprivation) have been associated with increased feelings of hunger and weight gain, lower ghrelin concentrations are found in subjects with manifest obesity. This paradoxic finding needs to be clarified. Longitudinal studies could help to deepen our understanding of long-term regulative processes in the secretion of ghrelin and associated phenomena.
- The majority of published clinical studies on ghrelin only investigated total ghrelin concentrations. However, acylated and non-acylated ghrelin are likely to have differential biological effects. By measuring total ghrelin concentrations the results mostly reflect the effect of non-acylated ghrelin that is found in much higher circulating concentrations in human blood. As non-acylated and acylated ghrelin might have converse biological effects, not only the absolute concentrations of each sub-form but also the ratio of non-acylated to acylated ghrelin might determine ghrelin's biological effects. In this context, the peptide obestatin, discovered as recently as 2005, needs to be mentioned: obestatin is derived form the same gene product (preproghrelin) as ghrelin. Hitherto only few studies focused on obestatin's biological functions that include regulation of sleep and feeding (Li *et al.*, 2011). The fact that obestatin is derived form the same gene product and is involved in the regulation of the same systems as ghrelin urges to investigate this peptide together with ghrelin.
- Protein concentrations determine the bioavailability of ghrelin due to protein binding of ghrelin in circulating blood. Differential protein binding patterns have been described for acylated and non-acylated ghrelin (Holmes *et al.*, 2009). This said, ghrelin concentrations are ideally interpreted in the context of blood protein concentrations. In addition, the activity of

the ghrelin o-acyltransferase (responsible for acylation of ghrelin) and also the degradation of ghrelin determine ghrelin's bioavailability.

- Ghrelin is produced mainly by the stomach. Most systems regulated by ghrelin, however, are located inside the CNS. Assuming that circulating ghrelin concentrations (and not only ghrelin produced locally inside the CNS) affect these higher brain functions, also the blood brain barrier penetrability determines ghrelin's biological effects.

11.8 Summary

In summary, ghrelin promotes sleep and induces a positive energy balance. Furthermore, ghrelin acts as a link between sleep and metabolism. The exact regulatory mechanisms (including reciprocal effects between ghrelin secretion, metabolism and sleep), the adaptive processes ghrelin secretion might undergo over time and the long-term consequences of its dysregulation are not yet completely understood. All the more reason to intensify the research on this fascinating peptide that will deepen our understanding of the regulation of basic biological functions. The availability of ghrelin (synthetic GHS-R ligands respectively) as potential therapeutic agent enhances ghrelin's attractiveness in biomedical research.

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Summary points

- Sleep plays an integral role in glucose homeostasis.
- Experimental studies have shown that acute or chronic partial sleep deprivation induces impaired glucose tolerance and insulin resistance in healthy subjects and patients with type 1 diabetes.
- Epidemiologic studies have provided evidence for an association between chronic sleep restriction and an increased risk of insulin resistance and type 2 diabetes. However, most of these studies relied on self-reported sleep measures.
- Sleep duration might be a target in the prevention of type 2 diabetes. Furthermore, sleep duration could become a therapeutic target to improve glucose regulation in patients with diabetes.
- A causal relationship between sleep restriction and insulin resistance has yet to be defined.

12. Partial sleep deprivation and insulin resistance

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Abstract

Sleep deprivation, as a consequence of voluntary sleep restriction or sleep disorders, has become endemic in our modern 24 hr society. Accumulating evidence from both experimental and epidemiologic studies suggests that sleep deprivation may represent an important risk factor for development of insulin resistance and diabetes. Several potential pathways could lead to insulin resistance after sleep restriction. However, a causal relation between sleep deprivation and insulin resistance remains to be defined. In this chapter, we will first discuss the impact of sleep on glucose metabolism and methods to assess insulin sensitivity. Subsequently, current data on the effect of sleep restriction on insulin sensitivity, will be discussed.

Keywords: glucose metabolism, insulin resistance, chronic sleep restriction

Abbreviations

FFA	Free fatty acids
IL-6	Interleukin 6
TNFα	Tumor necrosis factor alpha

12.1 Introduction

Sleep curtailment has become an increasingly common condition in our modern society. Sleep disorders such as insomnia or obstructive sleep apnea are more prevalent, leading to decreased sleep duration and sleep quality. However, much of the reduction in mean sleep duration is caused by voluntary sleep restriction. More than 40 years ago, the median sleep time in the United States in adults was ~8 hrs per night. Nowadays, median sleep time has decreased to ~7 hrs per night, with more than 30% of adults sleeping fewer than 7 hrs (Sleep in America Poll, 2003).

Interestingly, the increased prevalence of type-2 diabetes mellitus has been accompanied by this parallel trend in sleep curtailment. Type-2 diabetes is preceded by insulin resistance and impaired glucose tolerance. Epidemiologic and experimental studies have provided evidence for sleep curtailment as a risk factor for insulin resistance and type-2 diabetes.

12.2 Sleep and glucose metabolism

Maintenance of a constant blood glucose level is essential for normal physiology in the body, particularly for the brain. The brain is unable to store or synthesize the amount of glucose required for normal cellular function (Robinson and Rapoport, 1986). In the fasting state, plasma glucose levels are dependent on the balance between glucose production by the liver (endogenous glucose production) and glucose utilization. The consolidation of human sleep to a single period requires adaptations to overcome an extended period of fast. Therefore, normal glucose homeostasis shows a diurnal pattern, in which circadian rythmicity and sleep play a key role. For example, the onset of slow wave sleep is characterized by decreased brain glucose utilization and stimulation of release of counter-regulatory hormones, leading to a decreased glucose tolerance. Glucose tolerance is the ability to properly metabolize glucose and maintain normoglycemia (Figure 12.1). In healthy subjects, glucose tolerance decreases from morning to evening, reaching a minimum in the middle of the night. This decrease in glucose tolerance is caused by a decreased insulin sensitivity and insulin secretion (Van Cauter *et al.,* 1991).

12.3 Insulin resistance and assessment of insulin sensitivity in humans

Insulin is released by the pancreatic beta cells and stimulates glucose uptake by insulin sensitive tissues. Hepatic or endogenous glucose production is inhibited by insulin. Furthermore, insulin inhibits the hydrolysis of triglycerides in adipose tissue, which affects plasma FFA levels. Insulin

resistance is defined as decreased sensitivity or response to actions of insulin. Insulin resistance is therefore characterized by reduced muscle glucose uptake, increased endogenous glucose production and increased levels of FFA (Figure 12.2).

Several direct and indirect methods are available for determination of insulin sensitivity in humans. The hyperinsulinemic euglycemic clamp is the reference standard for directly determining insulin sensitivity. Briefly, a continuous infusion of insulin in a supraphysiological dose is used to suppress hepatic glucose production. A variable infusion of glucose is used to maintain or
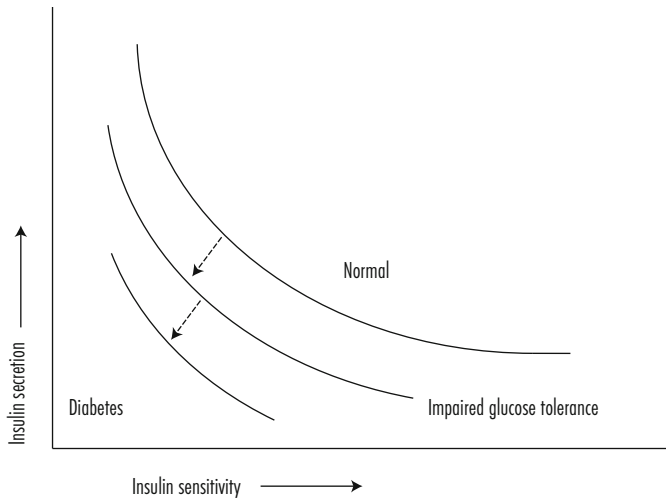
Figure 12.1. Schematic overview of relation between insulin release by pancreatic β-cells and insulin sensitivity. Insulin changes in response to insulin sensitivity to maintain normal glucose tolerance. Impaired glucose tolerance and finally diabetes occur when β-cell compensation is insufficient.
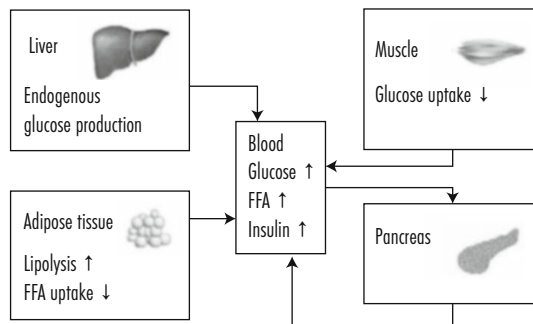
Figure 12.2. Features of insulin resistance. Insulin resistance is defined as decreased sensitivity or response to actions of insulin. Insulin resistance is characterized by reduced muscle glucose uptake, increased endogenous glucose production and increased levels of free fatty acids (FFA).

'clamp' fasting plasma glucose levels. A steady state is reached after a certain amount of time, in which the glucose infusion equals the glucose disposal by peripheral tissues. Insulin sensitivity is calculated from the mean glucose infusion rate during steady state conditions (DeFronzo *et al.*, 1979). Subjects with less peripheral glucose uptake are thus more insulin resistant. However, the hyperinsulinemic euglycemic clamp is a labor and time intensive method, which is not suitable for application in large study samples.

An alternative method is the glucose tolerance test, which indirectly measures insulin sensitivity. Either an oral or intravenous glucose load is given, after which blood samples are taken at intervals during the next 2 hrs for plasma glucose and insulin measurements. Insulin sensitivity is assessed by calculating the area under the curve for glucose and insulin and the insulin sensitivity index. The rate of glucose disappearance is decreased in insulin resistant subjects, reflected by an increased area under the curve for plasma glucose and decreased insulin sensitivity index.

The Homeostasis Model Assessment is a simpler tool to assess insulin sensitivity and can be used in large epidemiological studies. This model estimates beta cell function and insulin resistance from fasting plasma and insulin concentrations. The feedback loop between the liver (hepatic glucose production) and the beta cell (insulin secretion) is central to the model (Muniyappa *et al.*, 2008).

12.4 Experimental studies on the effect of sleep deprivation on glucose metabolism

Decreased glucose tolerance was already found in early studies using a model of total sleep deprivation for a prolonged period (Table 12.1) (VanHelder *et al.*, 1993). However, little attention was paid to these observations, since prolonged total sleep deprivation was considered to be an unlikely and non physiological condition. The first study that assessed the effect of recurrent partial sleep deprivation was performed by Spiegel *et al.* (1999). Sleep was restricted to 4 hrs per night for 6 consecutive nights in 11 healthy young men. Glucose tolerance was decreased by 40% after 6 nights of partial sleep restriction, which resembles glucose tolerance in ageing people with impaired glucose tolerance (Spiegel *et al.*, 1999). Another study proved that a less severe intervention of bedtime restriction to 5.5 hrs per night for 14 days in middle aged adults also decreased glucose tolerance and insulin sensitivity (Nedeltcheva *et al.*, 2009). Only one study reported no effect of chronic partial sleep restriction of 1 hr per night on glucose tolerance (Zielinski *et al.*, 2008).

Not only recurrent partial sleep restriction, but also a single night of partial sleep restriction affected insulin sensitivity. In 9 healthy subjects and 7 patients with type-1 diabetes, hyperinsulinemic euglycemic clamp studies were performed after one night of sleep restriction to 4 hrs and one night of normal sleep. Partial sleep restriction during a single night resulted in a 20-25% reduction in peripheral glucose uptake, compared to a night of normal sleep. In addition, plasma FFA levels and hepatic glucose production were increased during clamp conditions after sleep restriction

Table 12.1. Overview of experimental studies on the effects of sleep deprivation on glucose metabolism (adapted from Donga *et al.*, 2010).

Study	Sample size	Sleep intervention	Insulin sensitivity	Results
VanHelder *et al.* (1993)	10 healthy males	Total sleep deprivation for 60 hrs	OGTT	no differences in plasma glucose response to OGTT 20% increase in resting plasma insulin levels after sleep deprivation
Spiegel *et al.* (1999)	11 healthy males aged 18-27 yr	Partial sleep deprivation for 6 nights, bedtime 4 hrs/night	IVGTT 24 h profile glucose and hormone concentrations	40% decrease in glucose tolerance after sleep deprivation
Zielinski *et al.* (2008)	40 healthy adults aged 50-70 yr	Time in bed restriction for 8 weeks, total sleep time 1 hr less/ night	OGTT	no significant effect on glucose tolerance
Nedeltcheva *et al.* (2009)	6 healthy males 5 healthy females nean age 39 yr	Partial sleep deprivation 14 nights, bedtime 5.5 hrs/night	OGTT IVGTT	10% increase in 2-hr glucose levels and 17.5% decrease in insulin sensitivity
Donga *et al.* (2010a)	5 healthy men 4 healthy women aged 23-62 yr	Partial sleep deprivation 1 night, bedtime 4 hrs/night	Hyperinsulinemic euglycemic clamp	19-25% decrease in insulin sensitivity in multiple metabolic pathways
Donga *et al.* (2010b)	7 patients with type-1 diabetes, 3 males mean age 44 yr	Partial sleep deprivation 1 night, bedtime 4 hrs/night	Hyperinsulinemic euglycemic clamp	14-21% decrease in insulin sensitivity in multiple metabolic pathways

OGTT = oral glucose tolerance test; IVGTT = intravenous glucose tolerance test.

(Donga *et al.,* 2010a,b). This may be particularly relevant for patients with diabetes, who are unable to compensate for changes in insulin sensitivity themselves, other than by adaption of their exogenous insulin. Sleep restriction may therefore have clinical implications for treatment of patients with diabetes.

The results of these studies stress the importance of sleep duration as a physiological determinant for insulin sensitivity and suggest that sleep restriction increases the risk for development of insulin resistance and type-2 diabetes mellitus.

12.5 Potential mechanisms linking sleep deprivation and insulin resistance

The mechanisms underlying the impact of sleep restriction on glucose homeostasis are not yet fully understood (Figure 12.3). There have been conflicting reports on the effect of sleep restriction on counter-regulatory hormones such as cortisol, growth hormone and catecholamines (Nedeltcheva *et al.,* 2009; Spiegel *et al.,* 1999). Apparently, partial sleep restriction does not cause endocrine changes that simply explain the induction of insulin resistance. Alternatively, it is possible that partial sleep restriction decreases insulin sensitivity by altering the activity of the autonomous nervous system. Spiegel *et al* reported an increased sympathetic activity after partial sleep restriction, as derived from heart rate variability recordings (Spiegel *et al.,* 1999). However, it is currently unknown to what extend sleep deprivation induces comparable increases in sympathetic activity in other tissues. Another potential mechanism for induction of insulin resistance after sleep restriction might be the influence on the neuroendocrine regulation of
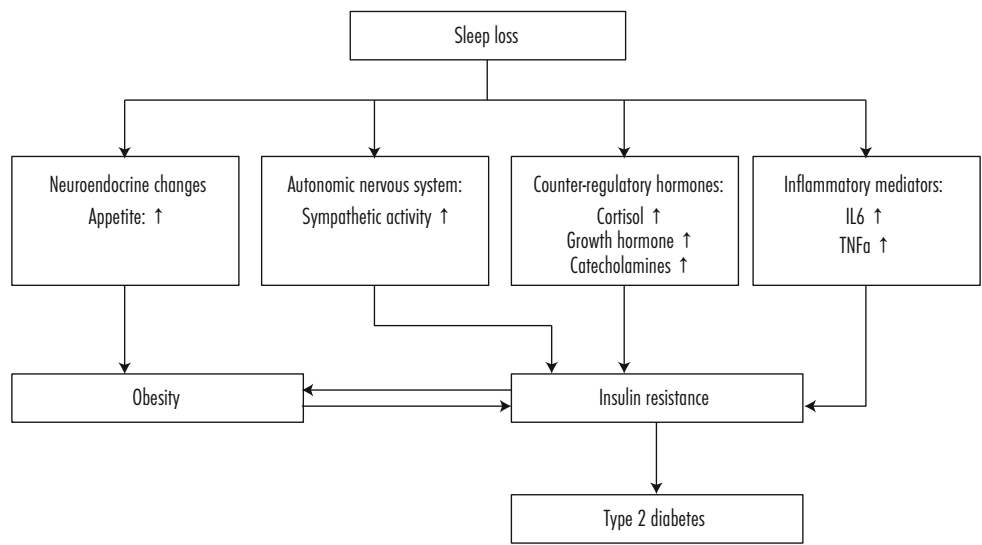
Figure 12.3. Potential mechanisms for insulin resistance after sleep deprivation (Knutson *et al.,* 2007).

appetite and food intake. A controlled laboratory study showed that partial sleep restriction altered appetite suppressing and –stimulating hormones, thereby increasing appetite and feelings of hunger (Spiegel *et al.,* 2004). In this way, sleep deprivation could lead to an increased risk of obesity and in turn, insulin resistance.

At last, inflammatory mediators, like TNFα and IL-6 are thought to be elevated after sleep restriction (Vgontzas, 2004). TNFα and IL-6 are both associated with insulin resistance. Taken together, changes in glucose metabolism caused by partial sleep restriction are likely to be multifactorial.

12.6 Epidemiologic studies of sleep duration and impaired glucose metabolism

Several longitudinal and cross sectional studies have found a U-shaped or J-shaped relation between sleep duration and impaired glucose metabolism and prevalence of type-2 diabetes mellitus. In the Sleep Heart Health Study, a self reported mean sleep duration of 6 hrs or less was associated with an odd ratio of 1.58 (95% CI 1.58-2.18) for impaired glucose tolerance, as assessed by an oral glucose tolerance test (Gottlieb *et al.,* 2005). A case-control study (Rafalson *et al.,* 2010) reported a threefold increased likelihood of developing impaired fasting glucose for participants sleeping 6 hrs per night or less. An important limitation of these two studies and other observational studies was that sleep duration was self reported and not objectively measured. The CARDIA Sleep Study used wrist actigraphy to objectively measure sleep duration (Knutson *et al.,* 2011). However, no association was found between sleep duration and fasting glucose, insulin or The Homeostasis Model Assessment index in 115 subjects without diabetes. Therefore, further research with objective measures of sleep duration is needed to better define the relation between sleep restriction and insulin resistance. Some potential subjects of further research could be:

- Cohort studies with objectively measured sleep parameters and glucose tolerance to establish a causal link between sleep duration and impaired glucose metabolism.
- Controlled trials with sleep promoting interventions to assess the effect on glycemic control in patients with diabetes.
- Studies on the effect of disturbed glucose metabolism on sleep parameters.

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Summary points

- Mammalian evolution has established reciprocal connections between sleep and energy homeostasis.
- Driven by the demands and opportunities of modern life many people sleep less than 6 hrs a night. Such short sleep has been associated with increased risk of obesity.
- Extended wakefulness has higher metabolic cost which leads to compensatory neuroendocrine, metabolic, and behavioral changes to stimulate food intake and conserve energy. These changes share principal similarities with the pattern of human metabolic adaptation to negative energy balance.
- Although this response may have evolved to offset the metabolic cost of extended wakefulness in habitats with limited food availability, it can become maladaptive in a modern environment which allows many to overeat while maintaining a sedentary lifestyle without sufficient sleep.
- Sleep-loss-induced metabolic adaptation can: (a) lead to increased retention of fat when people aim to return to their usual weight after life events associated with excessive food intake; and (b) undermine the success of behavioral interventions involving decreased food intake and increased physical activity to reduce metabolic risk in obesity-prone individuals.
- Overweight and obese individuals attempting to reduce their caloric intake and maintain increased physical activity should obtain adequate sleep.

13. Sleep deprivation and human energy metabolism

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Abstract

Driven by the demands and opportunities of modern life many people now sleep less than 6 hrs per night. In the sleep clinic, this behavior may present as a diagnosis of insufficient sleep syndrome (ICSD-9, #307.49-4) which is receiving increased attention as a potential risk factor for obesity and related metabolic morbidity. A central theme of this chapter is the notion that extended wakefulness has higher metabolic cost, which triggers a set of neuroendocrine (e.g. more hunger and less satiety), metabolic (e.g. lower resting metabolic rate), and behavioral (e.g. reduced daily activity) adaptations aimed at increasing food intake and conserving energy. Although this coordinated response may have evolved to offset the metabolic demands of sleeplessness in natural habitats with limited food availability, it can become maladaptive in a modern environment which allows many to overeat while maintaining a sedentary lifestyle without sufficient sleep. Growing experimental evidence now suggests that such sleep-loss-related metabolic adaptation could: (a) lead to increased retention of fat when people aim to return to their usual weight after various life events associated with excessive food intake; and (b) undermine the success of therapies combining reduced food intake and increased physical activity to decrease metabolic risk in obesity-prone individuals. Emerging observational and clinical trial data are consistent with this experimental framework, making it prudent to recommend that overweight and obese individuals attempting to reduce their caloric intake and maintain increased physical activity should obtain adequate sleep and seek effective treatment for any coexisting sleep disorders.

Keywords: insufficient sleep, food intake, energy expenditure, physical activity, obesity

13.1 Introduction

Multiple heritable and non-heritable factors, such as age, sex, race/ethnicity, environmental and socioeconomic conditions (geographic latitude, work schedules, poverty, etc.), physical health, and psychological wellbeing contribute to the epidemiologic variability in habitual sleep duration. The need to balance energy intake and expenditure is also linked to the quantity and quality of sleep, which contributes to the adaptation and metabolic survival of the organism in diverse natural habitats. Accordingly, daily sleep quotas of various animal species factor in variables such as basal metabolic rate, caloric density and macronutrient composition of the usual diet, and the ease and safety of its procurement.

Experimental data indicate that, on average, 7 to 8 hrs of nighttime sleep is needed to optimize human neurobehavioral performance. Driven by the demands and opportunities of modern life many people habitually sleep less than 6 hrs a night and epidemiologic studies show an association between such short sleep and increased risk of obesity (Chaput *et al.*, 2007; Garaulet *et al.*, 2011a; Nishiura *et al.*, 2010). A person can achieve and maintain energy balance at various levels of adiposity and with different amounts of food intake and matching energy expenditure. Under pressure from an environment which promotes overeating and physical inactivity, a large number of people in developed societies achieve energy balance when their body weight exceeds the recommended healthy range (Hill *et al.*, 2003). Whether lack of sufficient sleep can increase the level of individual adiposity in this context is an important question which is attracting increased research interest.

The inherent complexity of the association between short sleep and obesity is illustrated by the existence of reciprocal connections between sleep-wake behavior and the systemic control of fuel availability (Penev, 2007) mediated in part by a central network of widespread orexin/hypocretin pathways (Carter *et al.*, 2009; Tsujino and Sakurai, 2009). For instance, weight gain in rodents kept in a safe environment with abundant supply of palatable food allows increased amounts of sleep, whereas food deprivation results in increased vigilance and sleep loss, presumably to help maximize food finding and bioenergetic survival. Similarly, part of the epidemiologic variability in human sleep duration is linked to genetic polymorphism in the SUR2 subunit of the adenosine triphosphate-sensitive potassium channel which senses the state of cellular energy metabolism (Allebrandt *et al.*, 2011). Observations in individuals with abnormal thyroid function and pathological or experimentally-induced disruption of food intake also indicate that human sleep can be influenced by changes in energy metabolism and metabolic substrate availability (Penev, 2007).

Looking for effects in the opposite direction, experimental sleep deprivation in *ad lib* fed rats results in negative energy balance and weight loss despite the presence of compensatory hyperphagia, demonstrating that sleep can play an important role in energy conservation, tissue maintenance, and metabolic survival in the face of environmental adversity (Penev, 2007). But does human sleep provide similar benefits and what is the impact of insufficient sleep on human energy metabolism? This chapter presents emerging data from human sleep deprivation

experiments, which indicate that the lack of adequate nighttime sleep can affect important daytime behaviors (food intake and physical activity) governing the balance between energy intake and expenditure (Figure 13.1). These findings shed new light on the paradoxical association between obesity and the loss of sleep as the single most energy-efficient human behavior. A central theme of this discussion is the notion that extended wakefulness has higher metabolic cost, which triggers compensatory neuroendocrine, metabolic, and behavioral changes to stimulate food intake and conserve energy. This coordinated response may have evolved to offset the metabolic cost of sleeplessness in an environment with limited food availability. However, it can become maladaptive in a modern environment which allows many to overeat while maintaining a sedentary lifestyle without sufficient sleep. Such sleep-loss-related metabolic adaptation could lead to retention of fat when people aim to return to their usual weight after various life events associated with excessive food intake and undermine the success of therapies which combine reduced-calorie diet and increased physical activity to improve the metabolic health of obesity-prone individuals. At the end, this discussion will highlight some important gaps, limitations, and controversies in our understanding of the metabolic consequences of chronic sleep insufficiency.

Sleep can influence important waking behaviors (e.g. food intake and physical activity) governing the balance between energy intake and expenditure, and modify the metabolic risk of obesity-prone individuals.

13.2 The increased metabolic cost of sleep loss

Sleep is the single most energy-efficient human behavior. This state of maximally reduced total energy expenditure is the result of sleep-imposed immobility and absent nutrition, which eliminates the energy cost of activity and food-related thermogenesis, accompanied by a 20-30% decrease in basal metabolic rate, since less energy is needed to support brain function, sympathetic activity, breathing, circulation, and core body temperature during sleep (Figure 13.2). Jung *et al.* (2011) quantified the energy that is conserved by young non-obese adults during 16 hrs of wakefulness and 8 hrs of nighttime sleep in a room calorimeter compared to a matching period of total sleep deprivation. Total energy expenditure was 32% higher during the 8-hr period
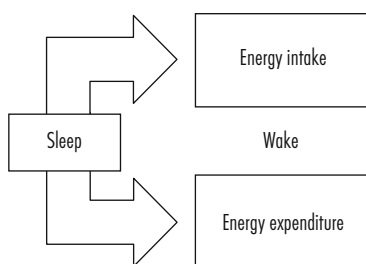
Figure 13.1. Metabolically relevant waking behaviors and sleep.
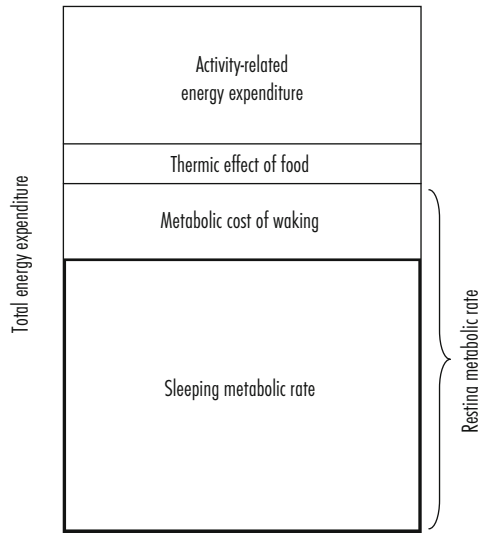
Figure 13.2. Human energy expenditure includes three principal components: (1) resting metabolic rate under basal conditions; (2) thermic effect of food (the cost of food assimilation equal to ~10% of total energy expenditure); and (3) activity-related energy expenditure (the energy used for all spontaneous and volitional daily activities). Sleep is a state of maximally reduced energy expenditure (thick line = sleeping metabolic rate) as a result of sleep-imposed immobility and absent nutrition, which eliminates the energy cost of activity and food-related thermogenesis, and a 20-30% decrease in resting metabolic rate, since less energy is needed to support brain function, sympathetic activity, breathing, circulation, and core body temperature during sleep.

without sleep and the average metabolic cost of sleep deprivation over 24 hrs was increased by ~135 kcal. If one extrapolates from these data ignoring any potential metabolic adaptation, a night with 1/3 less sleep (5.3 instead of 8 hrs) should increase 24-hr energy expenditure by 45 kcal/day – a metabolic cost which is sufficient to offset the positive 'energy gap' and prevent weight gain in ~90% of the population in developed societies (Hill *et al.*, 2003). Clearly, this simple arithmetic is incompatible with available epidemiologic data and does not reflect the complexity of the relationship between sleep loss and human energy metabolism.

A robust system of coordinated neuroendocrine, metabolic, and behavioral defenses is activated when human energy expenditure exceeds the corresponding amount of food intake. The observed changes include lower anorexigenic (leptin, insulin) and higher orexigenic (ghrelin) hormone concentrations to increase hunger, reduce satiety, and stimulate food intake, combined with lower sympathetic tone, reduced resting metabolic rate, and decreased activity-related metabolic expenditure to conserve energy (Rosenbaum and Leibel, 2010; Sumithran *et al.*, 2011). Together, these metabolic adaptations provide potent opposition to the threat of weight loss and depletion of body energy stores, and create ideal conditions for efficient retention of fat in both lean and obese individuals (Dulloo *et al.*, 2002; Rosenbaum and Leibel, 2010). From a clinical point of view, such increases in appetite and metabolic efficiency pose significant challenges

to the success of therapies which combine caloric restriction and increased physical activity to ameliorate metabolic risk in obesity-prone individuals (Rosenbaum and Leibel, 2010; Sumithran *et al.*, 2011).

Today, growing experimental evidence indicates that the changes in human energy metabolism in response to insufficient sleep share principal similarities with the human metabolic adaptation to negative energy balance (Figure 13.3). This concept first emerged in studies of overweight and obese adults who were treated with a 14-day hypocaloric diet twice in random crossover fashion (Nedeltcheva *et al.*, 2010b). Interventions were carried out in the laboratory with fixed time-in-bed (5.5 vs. 8.5 hrs/night) and caloric deficit of ~680 kcal/day to assess the effects of insufficient sleep on diet-induced changes in body weight, adiposity, energy expenditure, substrate utilization, and hunger. Participants lost ~1.0 BMI unit of body weight during each treatment, but lack of sufficient sleep reduced the amount of weight lost as fat by 55%. Thus, subjects defended their energy balance more vigorously when they did not obtain enough sleep and energy-dense fat was conserved albeit at the expense of 60% greater loss of less-calorically-dense and metabolically-costly-to-maintain lean body mass. Other neuroendocrine, metabolic, and behavioral changes in response to sleep loss included enhanced hunger, higher orexigenic (ghrelin), and lower
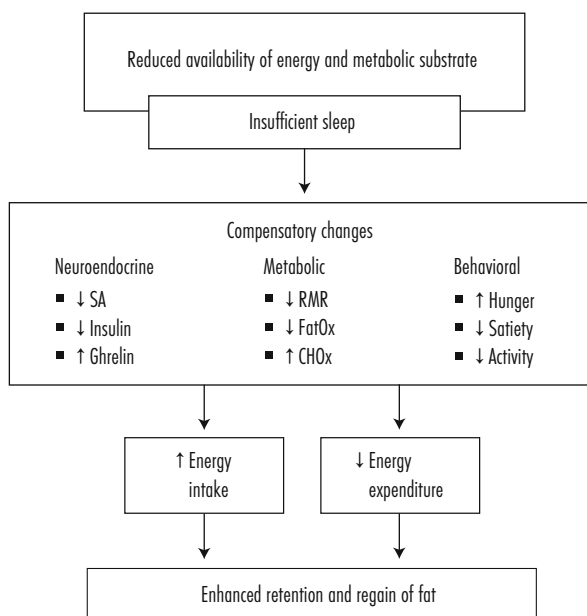
Figure 13.3. A schematic diagram of the concept that insufficient sleep triggers a set of neuroendocrine, metabolic, and behavioral adaptations aimed at increasing food intake and conserving energy.

SA = sympathetic activity; RMR = resting metabolic rate under basal conditions; FatOx = fraction of energy derived from fat oxidation; CHOx = fraction of energy derived from oxidation of carbohydrate; RQ = respiratory quotient.

anorexigenic (insulin) hormone concentrations, combined with signs of decreased sympathetic activity (lower plasma epinephrine) and resting metabolic rate (independent of the changes in body composition) to conserve energy. Measurements obtained after a single night of total sleep deprivation also suggest that the higher energy cost of additional wakefulness can lead to compensatory declines in resting metabolic rate on the following morning (Benedict *et al.*, 2011) and energy expenditure during a subsequent night of recovery sleep (Jung *et al.*, 2011). Compensation for increased activity-related energy expenditure due to experimental sleep fragmentation was also seen in respiratory chamber experiments, where 24-hr energy expenditure did not change despite the additional metabolic cost of multiple nighttime awakenings (Hursel *et al.*, 2011). Likewise, individuals exposed to longer periods of recurrent sleep restriction under controlled laboratory conditions did not show evidence of increased 24-hr energy expenditure that was measurable using doubly labeled water (Nedeltcheva *et al.*, 2009, 2010b; St-Onge *et al.*, 2011).

13.3 Insufficient sleep and changes in physical activity

The aparent adaptation in 24-hr energy expenditure in response to sleep loss suggests that the metabolic cost of extended wakefulness may be offset by declines in resting as well as non-resting (i.e. activity-related) energy expenditure. Limited by the reliability of subjective recall and differences in study design and population, cross-sectional analyses of sleep and physical activity have given inconsistent results showing either positive, negative, or no significant association. Few studies have tested the effect of sleep deprivation on the amount and intensity of daily activity. Roehrs *et al.* (2000) found higher percentage of inactivity in laboratory settings after one night of total sleep deprivation. Schmid *et al.* (2009) reported that overnight sleep restriction reduced the amount and intensity of free-living activity on the following day. In contrast, Brondel *et al.* (2010) found that a night with restricted sleep was followed by a day with increased food intake and more movement, while Bosy-Westphal *et al.* (2008) did not find effects of sleep restriction and higher food intake on daily activity. Finally, St-Onge *et al.* (2011) studied healthy lean adults exposed to 5 nights with fixed time-in-bed (4 vs. 9 hrs/night) and inadvertent caloric restriction (average deficit of ~400 kcal/day until night 4 followed by *ad lib* food intake after that): average daily activity recorded after nights 1, 2, 4 and 5 night (night 3 was followed by daylong bed rest) did not differ between sleep conditions. Interpreting the results of these studies is challenging, since they involved only acute sleep deprivation and did not control food intake to ensure that participants' energy balance was maintained. The impact of insufficient sleep on activity-related energy expenditure may differ as individuals adapt to recurrent exposure (Carter *et al.*, 2009; McEwen and Wingfield, 2011) and such brief interventions cannot capture the changes in physical activity of people who exercise only a few times a week. Furthermore, the amount of human activity can change in response to positive or negative energy balance (Rosenbaum and Leibel, 2010).

To explore the hypothesis that reduced movement contributes to the association of insufficient sleep with obesity, we examined the relationship between habitual sleep and daily activity in urban adults with parental history of type-2 diabetes (Booth *et al.*, 2012). Free-living activity

counts and time spent in sedentary, light, moderate, and vigorous-intensity physical activities measured by accelerometry were compared between matching groups of participants with habitual sleep <6 vs. ≥6 hrs/night measured by wrist actigraphy. Compared to participants who slept ≥6 hrs/night, short sleepers had 27% fewer daily activity counts, spent less time in moderate-plus-vigorous physical activity (-43 min/day), and were more sedentary (+69 min/day). To test whether insufficient sleep can be a causal factor for the reduced physical activity in short sleepers, a similar group of 18 subjects with parental history of type-2 diabetes completed one week of experimental sleep restriction in the laboratory (time-in-bed 5.5 hours/night) and a matching period with 8.5-hr nighttime sleep opportunity in randomized crossover fashion (Bromley *et al.*, 2011). Participants received a controlled weight-maintenance diet (0.5-0.6% body weight variability during each sleep condition) and those who exercised regularly at home could follow their usual exercise routines. Sleep restriction decreased daily activity by 31% as participants spent 24% less time engaged in moderate-plus-vigorous-intensity physical activity and became more sedentary. Most of the decrease in physical activity during the 5.5-hr time-in-bed condition was seen in individuals with regular exercise habits (-39% vs. -4% decline in exercisers vs. non-exercisers). On average, they re-allocated 30 min of daily moderate-plus-vigorous-intensity activity to less intense light and sedentary behaviors when their sleep was curtailed. Preliminary estimates of energy balance in ongoing studies where such habitual exercisers are exposed to 2 weeks with time-in-bed of 5.5 vs. 8.5 hrs/night suggest that insufficient sleep is accompanied by combined reduction in resting and activity-related energy expenditure of ~250 kcal/day – an amount equivalent to 60 min of moderate physical activity at 3.6 metabolic equivalent for the average study participant. The clinical significance of such reduced energy expenditure is readily apparent, since current guidelines recommend one hour of daily moderate-intensity physical activity for the prevention of long-term weight gain. Estimates of energy balance based on changes in body composition suggest that overweight and obese adults placed on a 2-week hypocaloric diet exhibit similarly large sleep-loss-related declines in resting and activity-related energy expenditure (Nedeltcheva *et al.*, 2010b).

13.4 Insufficient sleep and changes in energy intake

Influential early experiments found lower plasma leptin and higher ghrelin concentrations in association with increased hunger and appetite in young men exposed to 2 nights of insufficient sleep and reduced caloric intake (1,500 kcal/day for the average 75 kg study participant) at the time of sampling (Spiegel *et al.*, 2004b). Decreased leptin concentrations were also seen during a period of sleep restriction in men whose caloric intake was reduced by ~30% the day before sampling (10 kcal/kg breakfast replaced by 1.2 kcal/kg bolus of intravenous glucose) (Spiegel *et al.*, 2004a). Supported by data from some (Chaput *et al.*, 2007; Taheri *et al.*, 2004), but not other observational studies (Hayes *et al.*, 2011; Knutson *et al.*, 2011), these reports have given rise to the popular notion that insufficient sleep activates hormonal signals of 'famine in the midst of plenty' to cause excessive food intake and weight gain. However, studies of acutely sleep deprived volunteers who were truly in the midst of plenty (i.e. given access to adequate or excess amounts of self-selected calories) found either stimulatory or no independent effects of sleep loss

on plasma leptin (Bosy-Westphal *et al.*, 2008; Omisade *et al.*, 2010; Pejovic *et al.*, 2010; Schmid *et al.*, 2009; Simpson *et al.*, 2010). Furthermore, experiments combining 2 weeks of sleep restriction with over- or underfeeding showed that sleep insufficiency did not affect the corresponding rise and fall in leptin, whereas ghrelin increased only in the presence of negative, but not positive, energy balance (Nedeltcheva *et al.*, 2009, 2010b). It also appears that acute sleep deprivation can sometimes increase ghrelin concentrations (Benedict *et al.*, 2011; Schmid *et al.*, 2008), possibly in response to increased overnight energy expenditure while fasting is maintained. These observations suggest that the early reports of lower leptin and higher ghrelin concentrations (Spiegel *et al.*, 2004a, 2004b) did not reflect the presence of 'famine in the midst of plenty', but the ability of sleep loss to amplify the human neuroendocrine response to caloric restriction (Nedeltcheva *et al.*, 2010b), and that sleep-deprived humans have a more vigorous response to threats of negative energy balance (Penev, 2007). In an inadvertent test of this hypothesis, St-Onge *et al.* exposed healthy men and women to 4 days with sleep opportunity of 4 vs. 9 hrs/night and unintended caloric restriction (average daily deficit of ~400 kcal) (2011). When participants slept less during the 4-day period of caloric restriction, their *ad lib* energy intake on day 5 was ~300 kcal higher than that after the same caloric restriction with an extended sleep opportunity. If operational under long-term free-living conditions, this enhanced response to caloric restriction may undermine the success of dietary weight-loss therapy in individuals with insufficient sleep – an intriguing possibility which is consistent with the emerging data from early clinical trials and epidemiologic observations (Chaput *et al.*, 2011; Elder *et al.*, 2012; Garaulet *et al.*, 2011b).

In addition to energy, sleep also conserves carbohydrate. Higher respiratory quotient measurements following sleep restriction (Bosy-Westphal *et al.*, 2008) and repeated disruption of sleep (Hursel *et al.*, 2011) suggest that partial sleep loss is associated with use of a greater proportion of energy from carbohydrate. Sleep restriction also caused a shift in substrate utilization towards oxidation of relatively more carbohydrate in overweight and obese adults placed on a 2-week hypocaloric diet (Nedeltcheva *et al.*, 2010b). The modest decline in fasting blood glucose and improved insulin economy in this setting (Nedeltcheva *et al.*, 2010a) resembled the human metabolic adaptation to reduced carbohydrate availability. These findings raise the possibility that increased use of carbohydrate in individuals with insufficient sleep may stimulate hunger and food intake at times of diminishing glucose availability at night and during the late postprandial period. Indeed, some studies suggest that higher respiratory quotient predicts future weight gain (Gluck *et al.*, 2011). In addition, Chaput *et al.* (2009) observed that self-reported shorts sleepers have more relative hypoglycemia at the end of an oral glucose tolerance test, which also predicted future weight gain. Lack of sleep could also increase snacking and energy consumption from fat and carbohydrate as a result of more extended exposure to environmental stimuli which promote overeating and changes in reward seeking behavior (Nedeltcheva *et al.*, 2009; Tsujino and Sakurai, 2009). In agreement with these possibilities, insufficient sleep has been associated with irregular eating habits, more snacking between meals, and late night eating (Garaulet *et al.*, 2011a; Gluck *et al.*, 2011; Nishiura *et al.*, 2010; Weiss *et al.*, 2010). Increased use of protein to support the extended metabolic needs of glucose-dependent tissues (Nedeltcheva *et al.*, 2010b) may be another factor which contributes to the reported association of insufficient sleep with increased consumption of protein from meat and other high-fat food items (Garaulet *et al.*, 2011a; Grandner *et al.*, 2010; Weiss *et al.*, 2010).

13.5 Limitations and areas of uncertainty

Descriptive studies of the relationship between insufficient sleep and energy balance are often limited by incomplete assessments of sleep quantity and quality, reliance on subjective reports, and lack of control for other important factors such as activity, physical and emotional health, co-existing sleep disorders, socioeconomic stressors, etc. The inconsistency between self-reported sleep and that measured by polysomnography and free-living actigraphy, makes it difficult to assess the true quantity and quality of habitual sleep and can lead to different conclusions depending on which measure is used for analysis. Reliance on a single question about sleep is equally problematic, since the answer can be influenced by co-existing depression, anxiety, sleep disorder or other health problems and reflect one or more aspects of participant's usual time-in-bed, perceived sleep duration, or subjective sleep quality. Indeed, emotional distress and complaints of poor sleep were important correlates of self-reported short sleep in the Penn State (Vgontzas *et al.*, 2008) and MONICA/KORA study cohorts (Meisinger *et al.*, 2007). Thus, psychological stress, anxiety, and depression accompanied by difficulty sleeping, overeating, and adoption of other unhealthy behaviors may be important contributors to the association between short sleep and obesity. On the other hand, primary insomnia characterized by central hyperarousal, adrenal and sympathetic hyperactivity, elevated brain glucose metabolism, and resting energy expenditure may trigger metabolic adaptations in energy intake and expenditure (Figure 13.3), and increase the metabolic risk of obesity-prone individuals (Figure 13.4). Obstructive sleep apnea can confound the association of insufficient sleep and obesity in a similar fashion. Besides loss of slow-wave and rapid-eye-movement sleep, this disorder involves recurrent hypoxia, frequent arousals, and nighttime hyperactivity of adrenal and sympathetic stress-response mechanisms with higher metabolic cost, which may lead to compensatory changes in daytime food intake and physical activity (Figure 13.3), and facilitate the retention of fat in affected individuals (Figure 13.4). Additional research is needed to characterize human energy balance, substrate metabolism, and responsiveness of neural regulatory mechanisms to key metabolic signals in various sleep disorders.

Interventional studies in the sleep laboratory have their own limitations including high cost, technical difficulty, and small sample size. The artificial setting of these experiments also limits most occupational, volitional, and incidental physical activities of the participants and their interaction with social and environmental factors, making it difficult to identify subgroups with differential susceptibility to the metabolic consequences of insufficient sleep. For example, the lack of sleep-loss-related changes in physical activity in respiratory-chamber settings (Hursel *et al.*, 2011; Jung *et al.*, 2011) may be due to the extreme sedentary nature of this environment, which minimized moderate and vigorous-intensity activity irrespective of the presence or absence of sleep loss. Another important problem in the laboratory stems from the prior lack of attention to the fact that allowing the presence of negative energy balance during the study can fundamentally alter the metabolic impact of insufficient sleep. Therefore, future investigations will require careful reporting and meticulous attention to the nutritional state of the study participants. Finally, most laboratory interventions are relatively brief and capture only the acute (<1 week) and sub-acute (<1 month) effects of sleep loss, rather than its long-term consequences
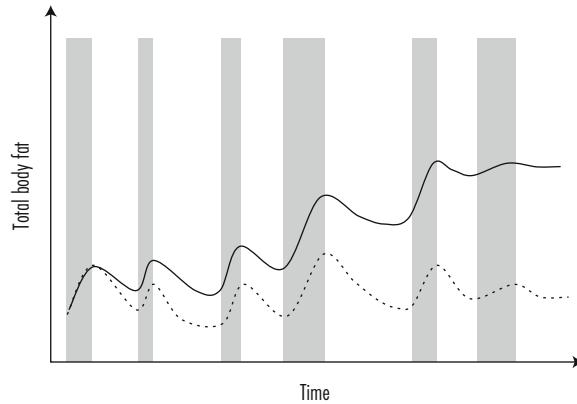
Figure 13.4. Insufficient sleep and retention of fat. Compared to the normal variation in body fat over time (dotted line), metabolic adaptation to chronic sleep loss, which enhances food intake and energy conservation to defend against negative energy balance, can lead to increased retention of fat (solid line) when people aim to return to their usual weight after various life events associated with excessive food intake (shaded areas). Although chronic sleep insufficiency may also promote more overeating at times of positive energy balance (e.g. related to relative carbohydrate depletion, extended exposure to the 'toxic' environment, changes in reward-seeking behavior, etc.), this is not required for the two lines to diverge.

which can be qualitatively and quantitatively different (Carter *et al.*, 2009; McEwen and Wingfield, 2011). Failure to recognize this can lead to erroneous long-term conclusions based on observations collected only during brief sleep interventions.

13.6 Guidelines

It has been argued that the modest increase in epidemiologic risk of obesity associated with short sleep is not a reason for concern (Horne, 2011). However, if causal, such modest effect of inadequate sleep can have considerable impact on public health since a large number of people sleep less than 6 hrs/night. Assuming that the weight gain related to a 2-hr reduction in daily sleep from 7 to 5 hrs/night 'could be worked off in very much shorter periods of brisk walking', it has been proposed that instead of trying to obtain sufficient sleep, overweight individuals should focus on 'more effective methods for weight reduction, such as comparatively brief periods of exercise' (Horne, 2011). However, engaging in more physical activity when sleep is insufficient may be easier said than done. Compared to urban adults who sleep ≥6 hrs/night, those who habitually curtail their sleep were more sedentary, had decreased amounts of daily movement, and spent less time in activities with moderate and vigorous intensity (Booth *et al.*, 2012). A similar behavioral pattern was produced by experimental sleep restriction to 5.5 hrs/night (Bromley *et al.*, 2011), suggesting that insufficient sleep can undermine the maintenance of regular physical activity and its health benefits. In addition, treatment with a hypocaloric diet resulted in reduced energy expenditure, decreased loss of fat, and more hunger when time-in-

bed was restricted to 5.5 hrs/night (Nedeltcheva *et al.*, 2010b), and sleep-deprived individuals ate more when *ad lib* food intake resumed after a few days of caloric restriction (St-Onge *et al.*, 2011). Along with emerging observational and clinical trial data in free-living adults (Chaput *et al.*, 2011; Elder *et al.*, 2012; Garaulet *et al.*, 2011b), these findings suggest that insufficient sleep can undermine the success of therapies combining reduced food intake and increased physical activity to decrease the metabolic risk of obesity-prone individuals (Figure 13.5). Although this novel concept requires further experimental support, it is prudent to recommend that overweight and obese individuals attempting to reduce their caloric intake and maintain increased physical activity should obtain adequate sleep and seek effective treatment for any coexisting sleep disorders.
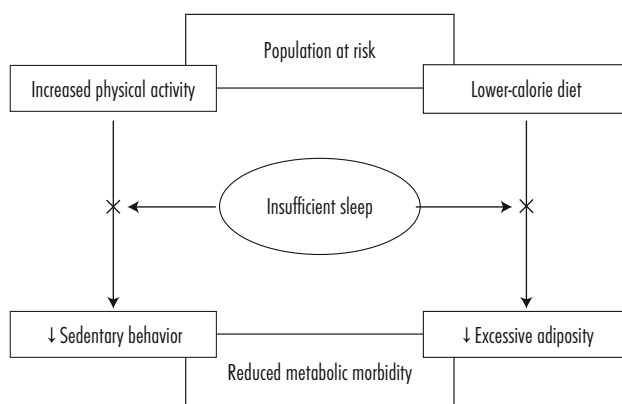
Figure 13.5. Insufficient sleep and metabolic disease prevention. Sleep-loss-related metabolic adaptations aimed at increasing food intake and conserving energy may compromise the adherence of obesity-prone individuals to therapies combining reduced food intake and increased physical activity, and promote efficient weight regain once they are discontinued.

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Summary points

- A sedentary activity is mainly characterized by low physical activity energy expenditure.
- Caloric intake may be proportionally related to the amount of time spent awake, especially if most of this time is spent doing sedentary activities, where snacking is generally more common.
- Greater increases in total energy intake (EI) were noted while watching television in comparison to listening to classical music or a control condition (i.e. no external stimuli).
- Greater increases in total EI were noted following one hour of seated video game playing in comparison to relaxing in a comfortable chair (control condition).
- Along with increases in mental stress, greater intakes of all macronutrients were noted following a cognitive task vs. relaxing in a sitting position.
- Increases in total energy, dietary fat and fluid intakes were noted during meals when music was on vs. no music.
- Television viewing, video game playing, cognitive working and music listening all lead to increases in energy and macronutrient intakes, but are not associated with increases in hunger and appetite sensations.
- A U-shaped relationship has been noted between sleep duration and changes in adiposity indicators.
- Short-duration sleepers with disinhibited eating behavior experienced a greater increase in body weight and waist circumference over a six-year follow-up period compared to short-duration sleepers with no disinhibited eating behavior.
- Short-duration sleepers (≤6 hrs per night) who increased their sleep time to 7-8 hrs/night experienced lower adiposity gains over time compared to those who did not increase their sleep duration.
- An interventional approach which concentrates on decreasing sedentary behavior rather than increasing physical activity participation may be warranted.
- Future studies should objectively evaluate non-exercise activity thermogenis in regard to sleep duration.

14. Sleep, sedentary activity and weight gain

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Abstract

The modern way of living is characterized by high participation in sedentary activities such as computing, watching television and playing video games. The practice of sedentary activities has been shown to have a negative influence on various indicators of health. Furthermore, the increase in energy intake observed while practicing sedentary activities is not related to increases in appetite or hunger sensations. As opposed to other sedentary activities, sleep may help facilitate the control of appetite and promote the maintenance of a healthy body weight. A U-shaped relationship has been noted between sleep duration and adiposity indicators, suggesting that both short- and long-duration sleepers are more likely to gain weight over time. Recent evidence shows that short-duration sleepers having a high disinhibition eating behavior trait are more at risk of gaining weight over time compared to short-duration sleepers having a low disinhibition eating behavior trait. In summary, it is important to make the distinction between 'sleep' and 'sedentary activities' when assessing their effects on health-related indicators. While most sedentary activities promote a positive energy balance, which may ultimately lead to weight gain over time, adequate sleep is rather associated with body weight stability and overall health.

Keywords: sedentary behavior, food intake, energy expenditure, sleep duration, obesity

J. McNeil, É. Doucet and J.-P. Chaput

Abbreviations

BMI	body mass index
EE	energy expenditure
EI	energy intake
MRI	magnetic resonance imaging
NEAT	non-exercise activity thermogenesis
PAEE	physical activity energy expenditure

14.1 Introduction

The increases in shift work and overtime hours, family and social demands, as well as time spent watching television and browsing the Internet (Alvarez and Ayas, 2004) have shaped a society which is functional 24 hours a day, 7 days a week. However, the decrease in sleep time required to accomplish these many demands may in turn lead to metabolic and health problems over time (Cappuccio *et al.*, 2008). Voluntary sleep restriction seems to be the main explanation for decreased sleep time in adults, where 43% of adults reported staying up later and sleeping less in order to watch television and/or use the Internet, while 45% of adults admitted to sleeping less in order to accomplish more work (National Sleep Foundation, 2002).

More closely related to the objective of this chapter is the observation that the practice of many sedentary activities, such as watching TV, playing video games and browsing the Internet, seems to create a positive energy balance, by promoting low PAEE and increasing EI. Through the effects of a decrease in PAEE and an increase in EI, sedentary behavior has been suggested to have a negative influence on certain cardio-metabolic markers, such as cholesterol and triglyceride levels, bone mass density and vascular health (Tremblay *et al.*, 2010). Even if sleep is considered to be the most sedentary of all human activities, it may in fact help facilitate appetite control and promote the maintenance of a healthy body weight (Chaput *et al.*, 2010). Furthermore, short sleep duration and/or lack of sleep, as well as disinhibited eating behavior and low calcium intake, have been suggested to play an important role in promoting obesity (Chaput *et al.*, 2009), highlighting the fact that weight gain is multi-factorial.

This chapter reviews the literature on the effects of sedentary behavior, such as TV viewing, video game playing, cognitive working and music listening, on energy metabolism, appetite control and weight gain. Furthermore, the relationship between sleep duration and weight gain is addressed, with an emphasis on behavioral factors such as non-homeostatic drives to eat and disinhibited eating behavior. Although alterations in sleep duration have also been shown to have an effect on certain neuro-endocrine hormones, which may lead to weight gain over time (Spiegel *et al.*, 2004), this chapter concentrates on behavioral factors which may affect sleep duration and, ultimately, adiposity indicators over time.

14.2 Modern sedentary activities and energy balance

In order to produce observable weight gain, a chronic positive energy balance needs to occur. A sedentary activity is mainly characterized by low EE, which includes prolonged time spent sitting in a car, at home, at work, or participating in certain leisure activities such as watching TV (Tremblay *et al.*, 2010). Additionally, caloric intake has been suggested to be proportional to the amount of time spent awake, especially if most of this time is spent doing sedentary activities, where snacking may be more common (Chaput *et al.*, 2010). And so, if spending more time doing sedentary activities promotes overconsumption of food, then a positive energy gap may easily be attained, thus potentially leading to weight gain over time if no adaptations occur. Several activities which are part of our daily schedule, such as TV viewing, video game playing, accomplishing mentally-demanding tasks (i.e. cognitive work) and music listening, have been shown to be associated to eating in the absence of hunger, i.e. regardless of appetite sensations (Table 14.1).

High levels of exposure to different types of media, including TV, video games and magazines, have also been correlated with lower self-esteem, fewer social interactions and increased aggression, suggesting that these activities may also have negative effects on one's psychological and social well-being (Holder *et al.*, 2009). Each of the activities presented in Table 14.1 are further discussed in the following sections.

14.2.1 Television viewing and video game playing

TV viewing is a very common sedentary activity at all ages, which accounts for a third to half of all sedentary activity time when compared to motorized transportation, homework, using the computer and playing video games (Biddle *et al.*, 2009). A positive relationship has been observed between TV viewing and obesity, which may be in part explained by a decrease in the time available to do physical activity and an increase in snacking while watching TV (Chaput *et al.*, 2010). TV viewing has also been suggested to promote obesity more so than other sedentary behaviors, such as sitting at work (Hu *et al.*, 2003) and lack of physical activity (Cameron *et al.*, 2003). Even though high BMI levels are often associated with increased TV viewing time, a causal link between TV viewing and obesity has yet to be established (Tremblay *et al.*, 2010). It may, however, be hypothesized that increased EI during TV viewing may be in most part due to an increase in the non-homeostatic drive to eat (Chaput *et al.*, 2010), such as certain cognitive, hedonic, social and environmental factors, since TV viewing stimulates food intake regardless of hunger feelings (Bellisle *et al.*, 2004). Along those lines, many individuals may also eat while watching TV because it is part of an habitual consumption pattern which has been developed over time (Chaput *et al.*, 2010). Lastly, TV viewing has been suggested to act as a 'distractor' which often encourages overconsumption by making the eater ignore important homeostatic, or satiety, signals (Bellisle *et al.*, 2004). Similar results have also been observed for video game playing, where this sedentary activity increased EI despite observing no increases in hunger sensations following one hour of video game play (Chaput *et al.*, 2011e). In summary, it may be hypothesized that increased EI during TV viewing and/or video game playing may be in most part

Table 14.1. Acute effects of certain sedentary activities on energy intake (adapted from Chaput *et al.*, 2010).

Author	Activity	Study design	Modality	Outcome
Blass *et al.* (2006)	TV viewing	Crossover study inside the laboratory	20 college students had *ad libitum* access to food during 30 minutes inside a room while watching TV vs. *ad libitum* access to food during 30 minutes while listening to classical music.	Greater increase in total EI (+ 1,069 kJ) while watching TV vs. listening to classical music.
Bellisle *et al.* (2004)	TV viewing and listening to a story on a cassette	Crossover study inside the laboratory	48 women had *ad libitum* access to food and water during 30 minutes inside a room while watching TV vs. *ad libitum* access to food and water during 30 minutes while listening to a story on a cassette vs. *ad libitum* access to food and water during 30 minutes with no external stimuli (control session).	Greater total EI during the TV viewing (+ 259 kJ) and listening to a story on a cassette (+ 293 kJ) sessions vs. the control session.
Chaput *et al.* (2011e)	Video game playing	Crossover study inside the laboratory	22 male adolescents took part in a one-hour session of video game play vs. a one-hour session of rest in a sitting position (control session). *Ad libitum* access to food afterwards.	Greater total EI (+ 335 kJ) in the lunch offered following the video game play session vs. the control session.
Chaput and Tremblay (2007)	Cognitive work	Crossover study inside the laboratory	15 female university students took part in a 45 minutes session of reading and writing vs. a 45 minutes session of rest in a sitting position (control session). *Ad libitum* access to food afterwards.	Greater absolute carbohydrate (+ 372 kJ), dietary fat (+ 444 kJ) and protein (+ 142 kJ) intakes following the reading and writing (cognitive work) session vs. control session.
Stroebele and de Castro (2006)	Listening to music	Observational study under free-living conditions	78 college students recorded food intake and environmental factors (e.g. music on or off and location) for seven consecutive days in a diary.	Greater energy (+ 447 kJ), dietary fat (+ 222 kJ) and fluid (+ 93 g) intakes when music was on. Meal duration was also longer when music was on (+ 11.26 minutes) vs. when music was off.

EI = energy intake

due to increased non-homeostatic drives to eat, which may ultimately increase food consumption through snacking (Nedeltcheva *et al.*, 2009). However, this potential causal relationship between non-homeostatic (e.g. cognitive, hedonic, social and environmental) factors and increased food intake during TV viewing and/or video game playing has yet to be established.

14.2.2 Cognitive work

Globalization and the addition of computers and new technologies have progressively led to the replacement of physical work by cognitive work as the main human modality in order to accomplish everyday tasks (Chaput *et al.*, 2011d). Additionally, the decreased energy cost of food procurement as a result of this transition has not been met with similar changes in eating patterns (Chaput *et al.*, 2010). As opposed to other types of sedentary activities, the use of computers and the increased mental demands at work and/or school has led to higher levels of stress in our everyday lives (Chaput and Tremblay, 2007). High stress levels have also been suggested to promote weight gain, which has been specifically demonstrated by Nakamura *et al.* (1998); noting a positive correlation between overtime hours and three-year increases in BMI and waist circumference in computer programmers, hardware designers and employees holding a clerical position. A study by Chaput and Tremblay (2007) also showed that increased heart rate, systolic and diastolic blood pressure, and stress levels were noted when the participants had to read and summarize a document using a computer vs. resting in a sitting position. Along with this increase in stress levels, greater absolute intakes of all macronutrients were noted following this cognitive task, while no increases in hunger ratings and energy expenditure were seen at this time. This thus suggests that increased hunger or energy expenditure do not explain this increase in EI following cognitive work, and that eating may in fact serve as a form of consolation to increased stress levels (Chaput *et al.*, 2010).

14.2.3 Listening to music

The development of new technologies has also led to an increase in the popularity of portable media and music players. Carlsson *et al.* (2005) have shown that listening to music was not more energy demanding when compared to complete silence. Additionally, Stroebele and de Castro (2006) noted an increase in total energy and fluid intakes during meals when music was on vs. when music was off. This increase in EI was mostly associated to increased fat intake, while carbohydrate and protein intakes were not significantly altered by the presence of music. These increases in energy and fat intakes were also more prominent when music was played in restaurants. However, music did not seem to have an effect on the distribution of EI (i.e. meal vs. snack intake) and no difference in this effect was noted between normal-weight and overweight participants. Music speed and volume were also not associated with meal size and duration, even though meal duration was longer when music was on and when more individuals were present (Stroebele and de Castro, 2006). Lastly, listening to music was not associated with increases in hunger or palatability ratings; once again emphasizing the importance of the potential effects of the non-homeostatic drives on energy and macronutrient intakes.

14.3 Sleep duration and energy balance

14.3.1 Sleep duration and adiposity indicators

A U-shaped relationship has been noted between sleep duration and changes in adiposity indicators in adults (Figure 14.1). This thus suggests that short- (i.e. ≤6 hrs) and long-duration (i.e. ≥9 hrs) sleepers are more prone to body weight and fat mass increases over time, in comparison to average-duration (i.e. 7-8 hrs) sleepers.

More specifically, Chaput *et al.* (2011c) recently observed that short sleep duration is associated with increases in abdominal adiposity in adults over a six-year follow-up period. This finding is of particular concern because abdominal adiposity is correlated with a number of metabolic anomalies. Causes of short sleep duration may be in part due to longer work days, increased night and shift work, as well as increased time spent watching TV and browsing the Internet (Alvarez and Ayas, 2004). Furthermore, short-sleep duration may promote a positive energy balance by increasing the amount of time available to eat, as well as amplify fatigue which may lead to a decrease in the motivation to exercise (Chaput *et al.*, 2008). These factors, as well as others which may potentially influence energy balance, are presented in Figure 14.2.
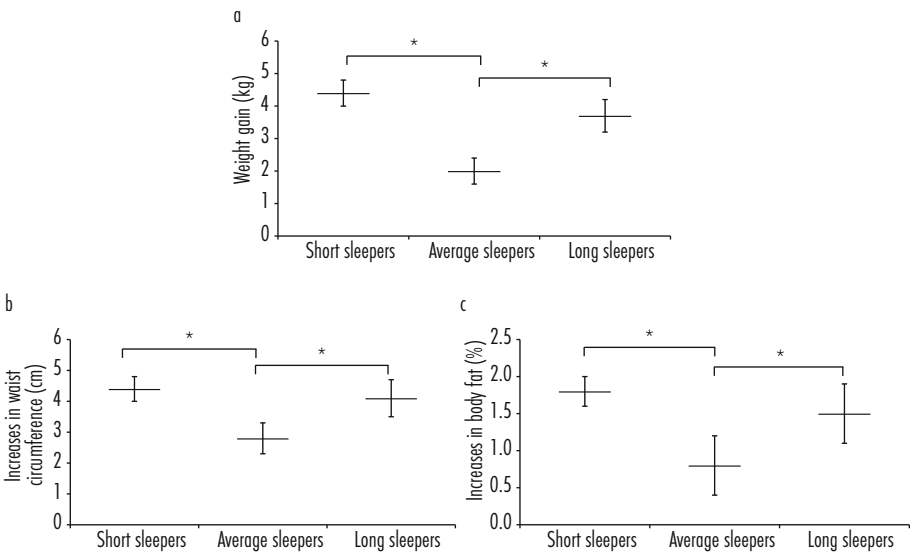
Figure 14.1. (a) Weight gain, (b) increases in waist circumference, and (c) increases in body fat percentage according to sleep-duration group. Values are presented as means for 117 men and 159 women with standard errors of the mean represented by vertical bars (adapted from Chaput *et al.*, 2008).
*Significant increase in weight, waist circumference and body fat percentage over time in short and long sleepers when compared to average sleepers ($P<0.05$).
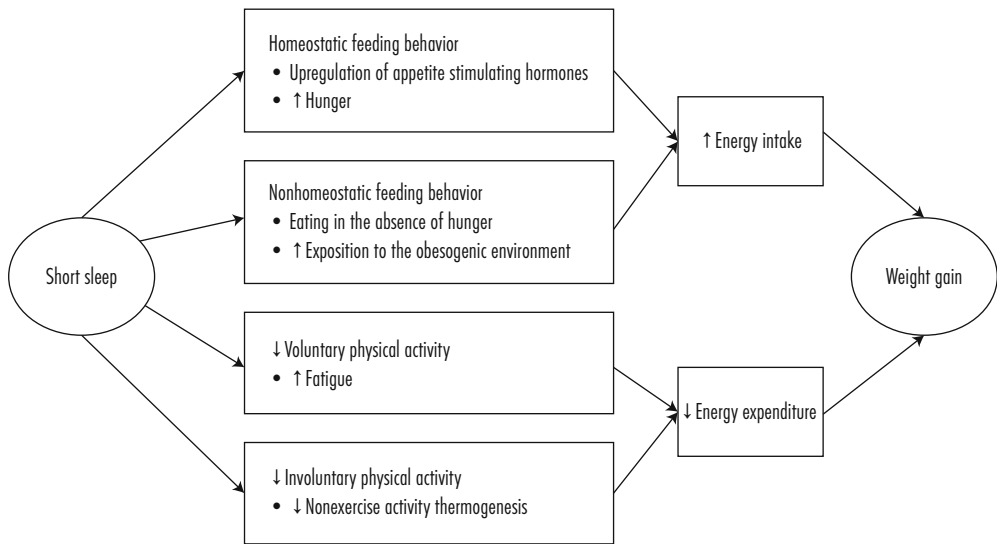
Figure 14.2. Potential mechanisms related to short-sleep duration which may lead to weight gain. This figure illustrates certain potential mechanisms by which short sleep duration may influence energy balance, by increasing energy intake and/or decreasing energy expenditure (Chaput *et al.* (2010), reproduced with permission. Copyright 2010 by Wolters Kluwer Health).

On the other hand, long-duration sleepers may have lower PAEE due to more time spent in bed, and may be more prone to sleep disorders which may lead to poorer sleep quality (Alvarez and Ayas, 2004). However, despite a U-shaped relationship between sleep duration and greater increases in weight and fat mass over time, there were no differences in demographic characteristics (e.g. educational level and annual income), resting metabolic rate and total EI between sleep duration groups, while short-duration sleepers reported more vigorous physical activity participation than did average-duration sleepers (Chaput *et al.*, 2008). Additionally, this study, in accordance with a study by Patel *et al.* (2006), noted that total EI and PAEE had no effect on the relationship between sleep duration and weight gain. This may be due to the limitations associated with the use of physical activity questionnaires and dietary recall methods, since many of these tools may not be accurate enough in capturing small energy gaps which may ultimately lead to weight gain over time (Chaput *et al.*, 2008).

14.3.2 Short sleep duration, cognitive dietary restraint and disinhibition eating behavior

Short sleep duration, low calcium intake, high disinhibition eating behavior trait and cognitive dietary restraint have all been associated with higher weight gain and a greater risk of developing obesity when evaluated during a six-year follow-up period in adults (Chaput *et al.*, 2009). As previously discussed, short-duration sleepers are more prone to weight gain and fat mass increases in comparison to average-duration sleepers. However, there also seems to be inter-

individual variations in weight gain among short-duration sleepers, thus encouraging further characterization of these individuals. Chaput *et al.* (2011a) partly explored this issue by measuring disinhibition eating behavior trait in short- (≤6 hrs), average- (7-8 hrs) and long-duration (≥9 hrs) sleepers.

As shown in Figure 14.3, short-duration sleepers with a high disinhibition eating behavior trait had a greater increase in body weight and waist circumference during a six-year follow-up period. Conversely, short-duration sleepers with a low disinhibition eating behavior trait had increases in these adiposity indicators which were similar to those seen in average-duration sleepers, suggesting that sleep-duration alone may not be sufficient to promote weight and adiposity gains over time. Additionally, total EI was highest in short-duration sleepers with a high disinhibition eating behavior trait. However, no difference in moderate-to-vigorous physical activity participation was noted between groups (Figure 14.4). Based on these results, disinhibited eating behavior is a risk factor which should be taken into consideration when assessing weight gain and the prevalence of obesity in short-duration sleepers. Lastly, short sleep duration has
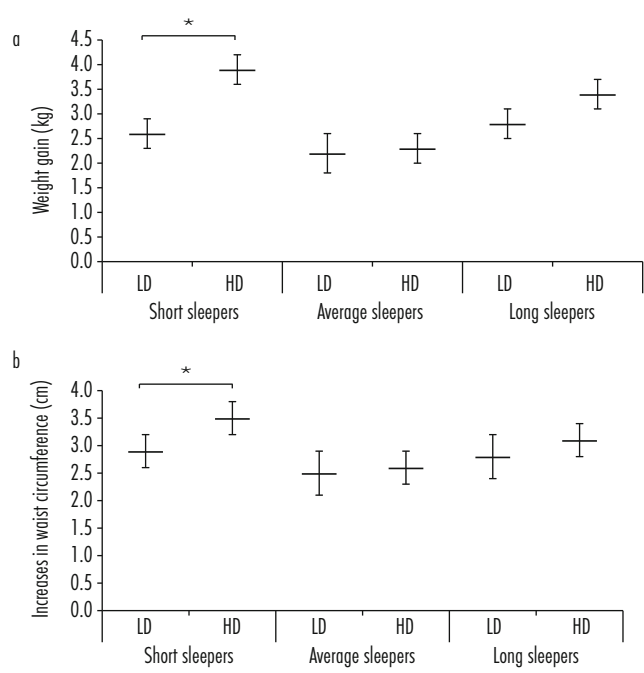
Figure 14.3. (a) Weight gain, and (b) increases in waist circumference according to sleep-duration group and disinhibition eating behavior trait (high vs. low). Low disinhibition (LD) eating behavior trait tertile (score≤3). High disinhibition (HD) eating behavior trait tertile (score≥6). Values are presented as means for 117 men and 159 women with standard errors of the mean represented by vertical bars (adapted from Chaput *et al.* (2011a)).
*Significant increase in weight and waist circumference over time in short sleepers with high disinhibition eating behavior trait when compared to short sleepers with low disinhibition eating behavior trait (*P*<0.05).
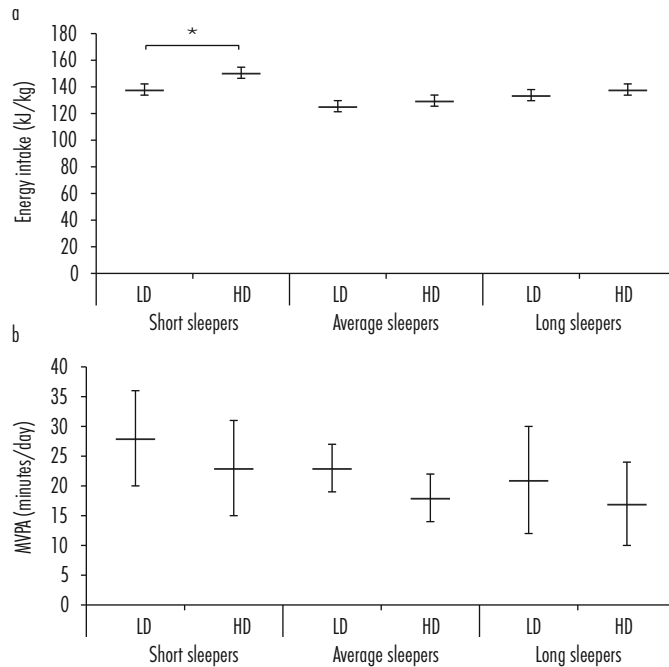
Figure 14.4. (a) Energy intake, and (b) moderate-to-vigorous physical activity (MVPA) participation according to sleep-duration group and disinhibition eating behavior trait (high vs. low). Low disinhibition (LD) eating behavior trait tertile (score≤3). High disinhibition (HD) eating behavior trait tertile (score≥6). Values are presented as means for 117 men and 159 women with standard errors of the mean represented by vertical bars (adapted from Chaput *et al.* (2011a)).
*Significantly greater energy intake in short sleepers with high disinhibition eating behavior trait when compared to short sleepers with low disinhibition eating behavior trait ($P<0.05$).

also been suggested to negatively affect stress responses and increase stress levels (Chaput *et al.*, 2011b). Along those lines, restrained eaters that are stressed seem to be more prone to overeating (Wardle *et al.*, 2000). And so, even though Chaput *et al.* (2011a) noted no significant interactions between sleep duration and cognitive dietary restraint, short-duration sleepers who are restrained eaters may be more prone to overeating and snacking, due to increased stress levels.

14.3.3 Short sleep duration, reward-driven eating behavior and snack intake

To date, only a few studies have looked at the possible relationship between reward-driven eating behavior and short sleep duration, and if this aspect of appetitive motivation may be in part responsible for the increases in snack intake previously noted following sleep restriction (Nedeltcheva *et al.*, 2009). More specifically, Nedeltcheva *et al.* (2009) observed an increase in snack intake following sleep restriction, despite no significant changes in total EI. Thus, the participants of this study may have compensated by decreasing their intake of other foods,

such as meal-type foods for instance, during the sleep restriction condition. Moreover, snack consumption was predominant between 7 pm and 7 am, suggesting that short-duration sleepers who stay up later at night may indeed be more prone to increased snack intake. Schmid *et al.* (2009) also noted an increase in snack intake following sleep loss in the absence of alterations in neuro-endocrine hormones (e.g. ghrelin and leptin), once again emphasizing the important role that non-homeostatic factors, rather than certain homeostatic signals, may have on food selection and food intake. It may also be suggested that short sleep duration may prevent adequate adaptation to food cues and important satiety signals. Through the use of functional MRI scans, Holm *et al.* (2009) noted a decreased reactivity in the ventral striatum, one of the primary reward centers of the brain, in adolescents with shorter sleep durations, decreased sleep quality and later sleep onset time when anticipating and receiving a monetary reward. However, it is not known whether this decrease in reactivity in the ventral striatum may also occur in adults, as well as in response to food cues. Hence, future studies would be needed to relate reward center activations in the brain in short-duration sleepers to food anticipation and food intake.

14.3.4 Interventions in short-duration sleepers: is extending sleep duration the solution?

In addition to establishing the short sleep-obesity connection (Chaput *et al.*, 2008), the corroboration and implementation of treatment guidelines which may aid in preventing body weight and fat mass gains over time in short-duration sleepers is essential. A longitudinal, observational study by Chaput *et al.* (2011b) noted that short-duration sleepers (≤6 hrs) who increased their sleep time to 7-8 hours/day had adiposity gains which were similar to average-duration sleepers (7-8 hours) when measured over a six-year follow-up period. Conversely, short-duration sleepers who did not change their sleep duration (i.e. chronic short sleepers) had a greater increase in BMI and fat mass, when compared to short-duration sleepers who increased their sleeping time (Figure 14.5).

Based on these results, increases in sleep duration (from short to average duration) seem to be associated with a lower adiposity gain over time. A randomized controlled trial is also currently under way, which measures the effects of an increase in sleep length on body weight and adiposity indicators in obese short-duration sleepers (Cizza *et al.*, 2010). Preliminary results from this study were published in 2010 and showed that the participants in the intervention group who have increased sleep duration reported a better mood and ability to focus, a decrease in sleepiness during the day, more willingness to exercise, as well as a decrease in caffeine intake and less cravings for sweet and salty foods during the evening. These preliminary results thus suggest that extending sleep duration may have beneficial effects on both mental and physical health in obese short-duration sleepers. Lastly, Rao *et al.* (2009) noted that a decrease in slow-wave sleep was associated with an increased incidence of obesity independent of sleep duration and efficiency. These results emphasize that future sleep intervention studies should also concentrate on increasing sleep quality and, more specifically, slow-wave sleep, rather than sleep duration alone. It is also important to target the root causes of voluntary sleep restriction; the reasons can be very different between individuals.
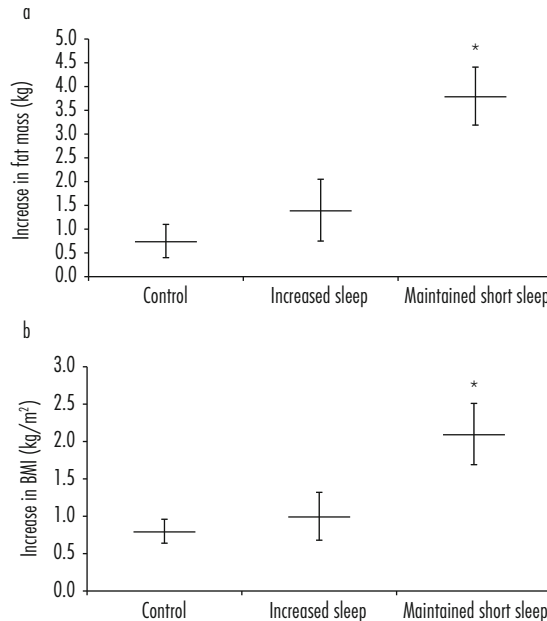
Figure 14.5. (a) Increases in body mass index (BMI) and, (b) increases in fat mass according to sleep-duration group. Control: individuals who reported sleeping 7-8 hrs/day at baseline and year six. Increased sleep: individuals who reported sleeping ≤6 hrs/day at baseline and 7-8 hrs/day at year six. Maintained short sleep: individuals who reported sleeping ≤6 hs/day at baseline and year six. Values are presented as means for 43 short-duration sleepers at baseline and 173 controls with standard errors of the mean represented by vertical bars (adapted from Chaput *et al.* (2011b)).
*Significant increase in body mass index and fat mass in individuals who maintained short sleep duration over time when compared to the control and increased sleep duration groups (*P*<0.05).

More subtle approaches, rather than directly altering total EI and structured physical activity participation, may also contribute to decreasing adiposity gains over time in individuals who spend a lot of time taking part in sedentary activities, such as watching TV, playing video games and cognitive work. An interventional approach which concentrates on decreasing sedentary behavior rather than increasing physical activity participation may be warranted. Reducing time spent doing sedentary activities may also be a more viable goal for many individuals in order to increase movement and EE (Tremblay *et al.*, 2010). Moreover, increasing non-structured physical activity (also called non-exercise activity thermogenesis or NEAT), such as taking the stairs at work and doing housework, may also aid in increasing movement and EE. Along those lines, short- and long-duration sleep may have potential negative effects on this EE component, which may then explain the increase in body weight and fat mass over time previously noted in these individuals (Chaput *et al.*, 2008), despite no significant changes in reported structured physical activity participation. However, this potential relationship has yet to be established, emphasizing that objective measurements of NEAT in sleep duration studies are needed (Chaput *et al.*, 2011d).

14.4 Conclusion

It has been well documented that the practice of sedentary activities, such as watching TV, playing video games and browsing the Internet promotes a positive energy balance by decreasing PAEE and increasing EI. Furthermore, the increase in cognitively demanding work has led to greater mental stress in many individuals, which also promotes excess EI. It is also relevant to note that these increases in EI while practicing sedentary activities is not related to increases in hunger sensations, suggesting that an increased EI while practicing these sedentary activities may be in most part due to an increase in the non-homeostatic drive to eat (Chaput *et al.*, 2010), such as certain cognitive, hedonic, social and environmental factors. Results from different studies suggest that this aspect of appetitive motivation may be in part responsible for the increase in energy-dense snack intake following sleep restriction. As such, the objective measurement of reward-driven eating behavior with motivational tasks and/or functional MRI brain scans in regard to food cues and food intake in short-duration sleepers is needed. As for long-duration sleepers, it is important to keep in mind that the presence of certain sleep-related disorders, poor sleep quality and increased time spent in bed, rather than the non-homeostatic drive to eat, may be the leading causes of weight and fat mass gains over time in these individuals (Chaput *et al.*, 2011a). All together, we need to make the distinction between 'sleep' and 'sedentary activities' when assessing their impact on health-related indicators. While most sedentary activities increase the positive energy gap that underlies weight gain, adequate sleep duration and sleep quality are rather associated with body weight stability and overall health. A good night's sleep is the 'normal' biological condition and should be further promoted as a critical health component.

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Summary points

- There is a growing body of evidence to support the belief that severe obstructive sleep apnea (OSA) is a risk factor for cardiovascular disease (CVD) and death.
- There appears to be a considerable overlap among factors related to CVD and those involved in metabolic syndrome (Mets) and OSA.
- Although age and the definition of hypopnea should be considered, recent population-based data showed a prevalence of more than 20% for apnea-hypopnea index (AHI) or respiratory disturbance index (RDI) ≥15.
- It has been reported that half of the OSA patients who should be treated have hypertension and that 30% of hypertensive patients have OSA that should be treated. In our recent population-based data from Japan, 26% of the hypertensive patients had an RDI≥15.
- Recent data from 3 countries, USA, China (Hong Kong) and Japan, showed that the prevalence of patients with diabetes whose AHI or RDI was ≥15 was greater than 30%
- In an urban male working population in Japan, sleep duration was significantly shorter in subjects with severe OSA than in subjects with non or mild OSA.
- It appears that over two-thirds of patients with severe OSA or an RDI≥30 have Mets in both Eastern and Western countries.
- One in 6 subjects with Mets, but only 1 in 40 subjects without Mets, had severe OSA in an urban male population in Japan.
- Associations between Mets as well as factors related to Mets and OSA, including short sleep duration, sleep fragmentation, and sleepiness should be studied further.

15. Metabolism, metabolic syndrome, obesity and sleep

Sleep apnea and metabolic syndrome in urban males

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Abstract

Obstructive sleep apnea and metabolic syndrome are significant risk factors for cardiovascular diseases. Several reports have shown that sleep duration also has a significant effect on body mass index and cardiovascular diseases. The relationships among obstructive sleep apnea, metabolic syndrome, components of metabolic syndrome, and sleep duration in 275 urban males in Japan were investigated. One in 6 subjects with metabolic syndrome, but only 1 in 40 without metabolic syndrome, had severe obstructive sleep apnea. Sleep duration was significantly shorter in subjects with severe obstructive sleep apnea (5.4±0.9 hrs) than in subjects with non (6.1±0.8 hrs: $P<0.05$) or mild obstructive sleep apnea (6.0±0.8 hrs: $P<0.05$). Mean sleep duration was significantly shorter in those with than without metabolic syndrome (5.8±0.8 hrs vs. 6.1 ±0.8 hrs: $P=0.026$) and was 5.3±1.1 hrs in metabolic syndrome subjects with severe obstructive sleep apnea and 5.9±0.8 ($P=0.021$) in metabolic syndrome subjects without severe obstructive apnea. Physicians should take into account the high prevalence of severe obstructive sleep apnea in patients with metabolic syndrome. Sleep duration should be considered as an important factor in studies investigating the prevalence of severe obstructive sleep apnea and metabolic syndrome.

Keywords: cardiovascular disease, diabetes mellitus, hypertension, sleep duration, sleepiness

Abbreviations

AHI	Apnea-hypopnea index
BMI	Body mass index
CPAP	Continuous positive airway pressure
CVD	Cardiovascular disease
HDL	High-density lipoprotein
Mets	Metabolic syndrome
NCEP	National Cholesterol Education Program
OSA	Obstructive sleep apnea
PM	Portable monitor
PSG	Polysomnography
RDI	Respiratory disturbance index
VFA	Visceral fat area

15.1 Introduction

Obstructive sleep apnea is characterized by repeated episodes of apnea and hypopneoa during sleep. In the textbook *Harrison's principles of internal medicine* it is stated, 'Obstructive sleep apnea/hypopnea syndrome (OSAHS) is one of the most important medical conditions identified in the last 50 years. It is a major cause of morbidity, a significant cause of mortality throughout the world, and the most common medical cause of daytime sleepiness.' The associations of obstructive sleep apnea/hypopneoa syndrome with cardiovascular and cerebrovascular events, diabetes mellitus, and liver were pointed out (Douglas, 2008). Thus, to control OSA is an important issue worldwide because the prevalence of OSA is high not only in Western countries but in Eastern countries (Al Lawti *et al.*, 2009; Nakayama-Ashida *et al.*, 2008). The NCEP Adult Treatment Panel III (2001) proposed a clinically-based approach that establishes a diagnosis of Mets when an individual has 3 of 5 risk factors for cardiovascular disease (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). These 5 characteristics are increased circumference (≥102 cm for men), systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg, increased fasting glucose ≥110 mg/dl, increased triglycerides ≥150 mg/dl, and decreased HDL cholesterol (<40 mg/dl). In another, a diagnosis of Mets was made using the Japanese criteria, namely, if the individual had a waist circumference ≥85 cm for men and ≥2 of the following risk factors: (1) increased triglycerides or decreased HDL cholesterol; (2) high blood pressure; (3) increased fasting plasma glucose.

There appears to be a considerable overlap among factors related to CVD and those involved in Mets and OSA. Several reports have shown that sleep duration has a significant effect on BMI, mortality, and diabetes (Al Lawti *et al.*, 2009). Recently, the relationship between Mets and sleep duration was reported (Choi *et al.*, 2008; Hall *et al.*, 2008;). In addition, it is said that the percentage of adults who sleep ≤6 hrs per day has increased markedly between 1985 and 2004 in parallel with a nationwide substantial increase in BMI (National Center for Health Statistics,

2005). From these data, it has been suspected that there may close relationships among OSA, Mets and sleep duration. In addition to findings of those reports, we will discuss the associations between OSA, Mets and its components, and sleep duration in urban males in Japan based on our recently published data (Chin *et al.*, 2010; Harada *et al.*, 2011, 2012; Nakayama-Ashida *et al.*, 2008). In these 4 reports (Chin *et al.*, 2010; Harada *et al.*, 2011, 2012; Nakayama-Ashida *et al.*, 2008), study subjects were male employees of an urban wholesale company in Japan. Of the 322 male employees who were first entered into the study (Nakayama-Ashida *et al.*, 2008), 275 were investigated further to examine the relationship between OSA, Mets, and several Mets-related factors (Chin *et al.*, 2010; Harada *et al.*, 2011, 2012) (Table 15.1). The BMI in this group matched that of general Japanese male populations. Based on NCEP and Japanese criteria, respectively, 68 (24.7%) and 58 (21.1%) of the 275 subjects had Mets (Table 15.1) (Chin *et al.*, 2010). This rate was

Table 15.1. Clinical features and comorbidities of 275 male subjects (Chin *et al.*, 2010).

	All subjects	No. OSA (RDI<5)	Mild OSA (5≤RDI<15)	Moderate OSA (15≤RDI<30)	Severe OSA (30≤RDI)	P value
No. of subjects	275	114	103	42	16	
RDI (/hr)	10.2±10.7	2.5±1.4	9.5±2.6*	20.4±3.3*	43.1±10.4*¶‡	<0.001
Age (years)	44±8	41±8	46±8*	47±7	47±7	<0.001
BMI (kg/m^2)	23.9±3.1	23.0±2.8	23.5±3.0	26.0±2.8*	27.5±2.4*¶	<0.001
Sleep duration (hrs)	6.0±0.8	6.1±0.8	6.0±0.8	6.0±0.7	5.4±0.9*¶	0.004
Epworth Sleepiness Scale	6.7±3.7	6.5±3.6	6.6±3.7	6.4±3.6	8.8±4.1	0.12
Waist circumference (cm)	83.6±8.5	80.8±7.9	83.3±7.6	88.6±8.3*¶	93.1±6.3*¶	<0.001
Blood parameters						
TC (mg/dl)	203±32	198±33	205±30	209±33	208±27	0.22
TG (mg/dl)	123±81	111±62	118±75	147±112	181±112*¶	0.002
HDL-cho (mg/dl)	57±14	57±15	60±13	54±12	49±13¶	0.011
Blood glucose (mg/dl)	104±22	100±15	104±18	108±22	119±56*	0.004
Dyslipidemia (n, [%])	91(33.1)	36(31.6)	32(31.1)	13(31.0)	10(62.5)	0.138
Hypertension (n, [%])	156(56.7)	57(50.0)	56(54.4)	31(73.8)	12(75.0)	0.004
Hyperglycemia (n, [%])	54(19.6)	17(14.9)	19(18.5)	13(31.0)	5(31.3)	0.017
Systolic BP (mm Hg)	129±14	127±14	130±15	132±12	132±11	0.21
Diastolic BP (mm Hg)	81±11	79±11	81±10	85±11*	84±6	0.0018
Prevalence of Mets, using:						
NCEP III citeria (n, [%])	68(24.7)	19(16.7)	24(23.3)	14(33.3)	11(68.8)	<0.001
Japanese criteria (n, [%])	58(21.1)	16(14.0)	19(18.4)	13(31.0)	10(62.5)	<0.001

*P<0.05, vs No OSA; ¶P<0.05, vs Mild OSA; ‡P<0.05, vs Moderate OSA.

OSA = obstructive sleep apnea; RDI = respiratory disturbance index; BMI, body mass index; TC = total cholesterol; TG = triclycerides; HDL-cho = high-density lipoprotein cholesterol; BP = blood pressure; Mets = metabolic syndrome; NCEP III = the National Cholesterol Education Program.

similar to that previously published (23.0%) for the general public in Japan. In addition, in 2007 in Japan, it was reported that the prevalence of hyperglycemia in male subjects in their 40s was 18.6%. Therefore, the prevalence of hyperglycemia in this study (19.6%) is similar to the general prevalence in Japan.

We determined sleep duration by actigraphy in conjunction with a sleep diary. Each subject was asked to wear an actigraph (Actiwatch AW-Light; Mini Mitter, Brend, OR, USA) for 7 days to estimate sleep-wake time, and a type 3 PM (Morpheus; Teijin, Tokyo, Japan, which is the same as Somte´; Compumedics, Victoria, Australia), an alternative to PSG in the diagnosis of OSA, for 2 nights at home. In this study, sleep duration was measured in home settings. The RDI (=number of apnea and hypopnea episodes per hour during analyzed time) was calculated from findings of both actigraphy and the PM. Records of the PM were inspected visually and scored by at least two medical doctors specialized in respiratory medicine. Apnea is defined as the cessation of breathing for at least 10 s and hypopnea as a more than 50% reduction in the amplitude of nasal pressure or respiratory effort associated with a more than 3% reduction in oxyhaemoglobin saturation for at least 10 s. Apnea and hypopnea were scored while researchers were blinded to other information except for sleep-wake time by actigraphy. Data without oxygen saturation values and illegible recordings were excluded from analysis. Data for <2 hrs were also excluded. When data from both recorded nights were available, records from the second night were analyzed further (Chin *et al.*, 2010; Harada *et al.*, 2011, 2012; Nakayama-Ashida *et al.*, 2008).

15.2 Obstructive sleep apnea

OSA is characterized by repeated episodes of apnea and hypopneoa during sleep. By consensus criteria, an apnea episode is defined as cessation of airflow for at least 10 s using a valid measure of airflow and a hypopneoa episode is present when 1 of the following 2 criteria are met: (1) ≥30% drop in airflow from baseline for at least 10 s with ≥4% desaturation from baseline; or (2) ≥50% drop in airflow for at least 10 s with ≥3% desaturation or an arousal (American Academy of Sleep Medicine, 2007). All AHI values were expressed as the number of episodes of apnea and hypopnea per hr over the total sleep time. OSA severity is most often defined by the AHI as follows: non or mild OSA (5≤AHI<15), moderate OSA (15≤AHI<30), and severe OSA (AHI≥30) (Report of American Academy of Sleep Medicine Task Force, 1999).

The prevalence of OSA is high not only in Western but also Eastern countries (Al Lawti *et al.*, 2009; Nakayama-Ashida *et al.*, 2008). In a famous study, Young *et al.* (1993) estimated that approximately 24% of men and 9% of women have sleep apnea (defined as an AHI5) and that 9% of men 4% of women have at least moderate disease (defined as an AHI≥15). It has been well known that the prevalence of OSA increase according to the gain in BMI, worldwide. Although age and the definition of hypopneoa should be considered, recent population-based data showed a prevalence of more than 20% for AHI or RDI≥15 (Gottlieb *et al.*, 2010; Nakayama-Ashida *et al.*, 2008).

It is said that the prevalence of OSA in patients with hypertension or diabetes is higher than in apparently healthy subjects. Individuals who had systolic blood pressure readings ≥140 mm Hg, diastolic readings ≥90 mm Hg, a history of a diagnosis of hypertension before the study measurements, or were currently using anti-hypertensive medications were defined as having hypertension. It has been reported that half of OSA patients who should be treated have hypertension and that 30% of hypertensive patients have OSA that should be treated (Somers *et al*., 2008). In our recent population-based data from Japan, 88 (32%) of 275 middle-aged males (age 44±8, mean±standard deviation) yrs, BMI 23.9±3.1 kg/m^2) in an urban city had hypertension and 26% (n=23) of the hypertensive patients had an RDI≥15 (Harada *et al*., 2011). The prevalence of hypertension among Japanese males in their 40s was 35.5% in 2006, which is similar to that in this study (32.0%). Therefore, our data are applicable to reflect the current situation in Japan.

The prevalence of OSA among patients with diabetes reported in the 4 studies that used the gold standard method of full PSG for OSA assessment and that defined OSA as an AHI≥5 events/h was consistently higher than 50% (average 73%) (Aronsohn *et al.,* 2010; Einhorn *et al.*, 2007; Foster *et al*., 2009; Resnick *et al*., 2003). Thus, studies in Western populations have found very high rates of OSA among subjects with diabetes, but diabetic individuals in Asian populations have a lower average BMI than those in Western populations. Since obesity is a strong risk factor for OSA, it is important to examine whether there are similar associations between the RDI and diabetes in an Asian population. There have been few reports of population-based studies from Asia where the prevalence of diabetes as well as that of OSA is interestingly compatible to that in the West (Chan *et al*., 2009; Ramachandran *et al.*, 2010). Recent data from 3 countries, USA, China (Hong Kong) and Japan, showed that the prevalence of patients with diabetes whose AHI or RDI was ≥15 was greater than 30% (Aronsohn *et al.*, 2010; Harada *et al.*, 2012; Lam *et al*., 2010). Thus, worldwide, there are huge numbers of patients with diabetes who might need treatment for OSA (Table 15.2).

There are much data about the relationship between intermittent hypoxia and lipid metabolism. However, the effect of OSA on dyslipidemia and lipid metabolism in humans remains to be fully established. Therefore, the effects of OSA on lipid metabolism should be studied more (Drager *et al*., 2011).

15.3 Obstructive sleep apnea and metabolic syndrome

Although the data were cross sectional, severe OSA has been recognized as a significant risk factor for CVD and mortality (Marin *et al*., 2005; Young *et al*., 2008). Moderate OSA is also thought to be a risk factor for CVD and death (Marshall *et al*., 2008). Recent prospective data also showed that severe OSA was a significant risk factor for CVD in middle-aged males (Gottlieb *et al.*, 2010). To treat and prevent Mets and OSA is thought to be a key factor in controlling the occurrence of CVD and reducing deaths from CVD. As obesity is the most important factor for both OSA and Mets, 5 recent studies showed that OSA was significantly associated with Mets (Coughlin *et al*., 2004; Gruber *et al.*, 2006; Lam *et al.*, 2006; Parish *et al*., 2007; Sasanabe *et al*., 2006). However, 4 of the 5 were non-epidemiological studies, while subjects in the one epidemiological study were

Table 15.2. Prevalence of OSA in DM in Japan, USA and China. About the characteristics of our subjects, 21 of 275 had diabetes. BMI of all the subjects was 23.4 and BMI of diabetic subjects was 25.9. The prevalence of OSA in diabetic subjects was 81%. The prevalence reported from USA and China was as shown.

	Japan	USA	China
Subjects	Population	Hospital/Clinic	Hospital/Clinic
n	21*/275**	60*	165*
Age (DM)	50.0	57.0	57.3
BMI (DM)	25.9	33.8	26.9
M/F	21/0	27/33	99/66
OSA	81%	77%	53.9%
Normal	19 (%)	23 (%)	46.1 (%)
Mild	47.6 (%)	38.3 (%)	21.1 (%)
Moderate	19 (%)	25 (%)	15.2 (%)
Severe	14.3 (%)	13.3 (%)	17.6 (%)
Desaturation (%)	3	4	4
	Harada, 2012	Aronsohn et al., 2010	Lam et al., 2010

OSA = obstructive sleep apnea, DM = diabetes mellitus, BMI = body mass index, Desaturation: level of least desaturation in hypopnea. *patients with diabetes, **subjects in an urban city in Japan.

relatively obese for an Asian population (Lam et al., 2006). Another study reported that obesity and not OSA was responsible for metabolic abnormalities (Sharma et al., 2007). From our data, the presence of Mets was primarily determined by obesity and age, and, to a lesser extent, by sleep apnea. Thus, it is not yet established whether Mets is primarily determined by obesity or sleep apnea (Chin et al., 2010). However, results of this study of an urban male working population also showed that the prevalence of Mets in severe OSA patients was nearly 70%, which is the same as that reported in previous studies (Coughlin et al., 2004; Gruber et al., 2006; Lam et al., 2006; Parish et al., 2007; Sasanabe et al., 2006). Therefore, it appears that over two-thirds of patients with severe OSA or an RDI ≥30 have Mets in both Eastern and Western countries. In addition, although the prevalence of OSA in Mets subjects is not well understood, conversely, the prevalence of Mets in subjects with OSA has been investigated several times. One in 6 subjects with Mets, but only 1 in 40 subjects without Mets, had severe OSA in an urban male population in Japan (Chin et al., 2010).

In an epidemiological study of a Japanese urban population of businessmen matched for body weight the following was found: (1) although there was a significant association between an increase in the proportion of Mets and the severity of OSA, the severity of OSA had no significant effect on the occurrence of Mets after data were adjusted for age and BMI; and (2) although BMI and age both had a significant effect, the prevalence of severe OSA in Mets subjects was higher than that in non-Mets subjects. Thus, there might be close relationships between visceral

fat and OSA (Chin *et al.*, 2010). However, results differed as to the effects of CPAP treatment on VFA; that is, a reduction in VFA following CPAP treatment was shown in two reports and no reduction in VFA was shown in two other reports (Chin *et al.*, 1999; Münzer *et al.*, 2010; Trenell *et al.*, 2007; Vgontzas *et al.*, 2008). In summary, results on this issue are contradictory, and more study is needed to clarify the relationships between VFA and OSA. Data from the most recent randomized clinical trials showed that in patients with moderate-to-severe obstructive sleep apnea syndrome, 3 months of CPAP therapy lowered blood pressure and partially reversed metabolic abnormalities (Sharma *et al.*, 2011).

15.4 Sleep duration, OSA, Mets, sleepiness, and sleep fragmentation

Sleep duration has fallen with technological advances and industrialization of society. The reduction in sleep times has been further accelerated by the increased prevalence of shift work and the development of 24-hr entertainment through television and the Internet (Al Lawti *et al.*, 2009). Data from the Centers for Disease Control and Prevention show that in every age group and in both genders there was an increase from 1995 to 2005 in the percentage of individuals sleeping <6 hrs per night (Colten and Altevogt, 2006). Among middle-aged adults, about 30% of the population reported sleeping less than 6 hrs per night (Colten and Altevogt, 2006). Our recent data for the 275 urban male subjects showed that their mean for sleep duration by actigraph was 6.0±0.8 hrs (Table 15.1) (Chin *et al.*, 2010). We found a significant negative correlation between RDI and mean sleep duration as measured by actigraph over a period of 1 week (r=-0.19, P=0.0016). Subjects with severe OSA had significantly shorter sleep duration than with non or mild OSA (P<0.05) (Table 15.1 and Figure 15.1a). Mean daily sleep duration in Mets subjects was significantly less than in
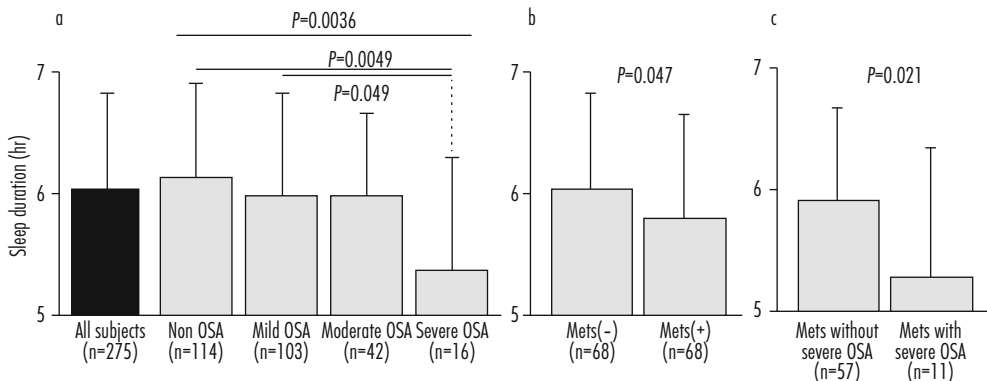
Figure 15.1. Weekly mean sleep duration in OSA and/or Mets subjects. (a) The relationship between the severity of OSA and the weekly mean sleep duration in bed, as measured by an actigraph. Only severe OSA significantly shortened sleep duration. (b) BMI- and age-matched subjects with Mets (n=68) and without Mets (n=68). (c) Mets with severe OSA (n=11) and Mets without severe OSA (n=57) (Chin *et al.*, 2010). OSA = obstructive sleep apnea; Mets = metabolic syndrome.

non-Mets subjects (5.8±0.8 hrs vs. 6.1 ±0.8 hrs: *P*=0.026). BMI- and age-matched subjects with (n=68) and without (n=68) Mets were compared because BMI and age were significantly related to the occurrence of Mets: there was a significant difference in sleep duration between subjects with and without Mets, but not in RDI (Table 15.3 and Figure 15.1b). Mean sleep duration was 5.3±1.1 hrs in Mets subjects with severe OSA and 5.9±0.8 (*P*=0.021) in Mets subjects without severe OSA (Figure 15.1c). In our studies, sleep duration was measured in home settings. In many studies sleep duration was assessed by overnight PSG in laboratory settings where subjects tended to sleep more poorly than at home. In addition, sleep duration was measured by actigraph for a week in the present study. Although most epidemiological studies use self-reported sleep duration, which may not be accurate, differences between actigraph-measured and subjective reported sleep durations were detected, and objectively measured sleep duration is recommended. Thus, in our studies, by using both actigraphy and a sleep diary under usual circumstances for a week, we could examine sleep duration accurately to explore the importance of adequate sleep. When we compared the relationships between sleepiness and OSA in subjects with or without hypertension, we found that short sleep duration was related to sleepiness both in the hypertensive and non-hypertensive subjects, but that the RDI was also related significantly to sleepiness independently of sleep duration only in the hypertensive subjects (Table 15.4 and Figure 15.2). In addition, we observed an inverse relationship between the RDI and sleep duration in the hypertensive subjects. Despite some conflicting results in interventional trials of treatment of OSA and hypertension, pre-treatment sleepiness is an important factor in determining a reduction in blood pressure after CPAP treatment (Barbé *et al.*, 2001; Robinson *et al.*, 2006). Thus, it is suggested that there is some relationship between sleepiness in OSA and the presence of hypertension. In addition to hypertension, sleepiness (Barceló *et al.*, 2008) and sleep duration (Spiegel *et al.*, 2009) have a significant effect on the glucose metabolism. It also has been reported that associations between hypertension and fasting plasma glucose and not sleep duration, but instead sleep fragmentation, were important (Knutson *et al.,* 2011). In the future, associations between Mets as well as factors related to Mets and OSA, including short sleep duration, sleep fragmentation, and sleepiness should be studied further (Figure 15.3) (Arnardottir *et al.*, 2009).

Table 15.3. Comparison of the background between 68 patients with Mets and 68 patients without Mets, matched for age and BMI (Chin *et al.,* 2010).

	Non-Mets	Mets	P value
No. of subjects'	68	68	
RDI(/hr)	12.7±10.2	15.7±14.2	0.16
Age (years)	46±8	46±7	0.94
BMI (kg/m^2)	26.0±2.4	26.1±2.6	0.78
Sleep duration (hr)	6.1±0.7	5.8±0.8	0.047
Epworth Sleepiness Scale	8.2±4.6	8.7±4.3	0.46

DRI = respiratory disturbance index; BMI = body mass index.

Table 15.4. (a) Univariate analyses of correlation coefficient among sleepiness assessed by ESS scores, the severity of OSA assessed by RDI and sleep duration. Multiple regression analyses to predict sleepiness assessed by ESS scores in subjects (b) with hypertension (n=88) and (c) without hypertension (n=187).

		Subjects with HT	Subjects without HT	
a	ESS score and RDI	0.33*	-0.01	
	ESS score and sleep duration	-0.30*	-0.18*	
	RDI and sleep duration	-0.29*	-0.13	
		β	γ	R^2(%)
b	RDI (/hr)	0.26	0.33	8.6
	Sleep duration (h)	-0.23	-0.30	6.9
	Cumulative R^2			15.5
c	RDI (/hr)	NA	NA	NA
	Sleep duration (h)	-0.18	-0.18	3.2
	Cumulative R^2			3.2

ESS = Epworth Sleepiness Scale; OSA = obstructive sleep apnea; RDI = respiratory disturbance index; HT = hypertension; NA = not applicable. In (a) data are expressed as correlation coefficient and *$P<0.05$; in (b) and (c) β = standard regression coefficient, γ = correlation coefficient and R^2 = contribution rate.
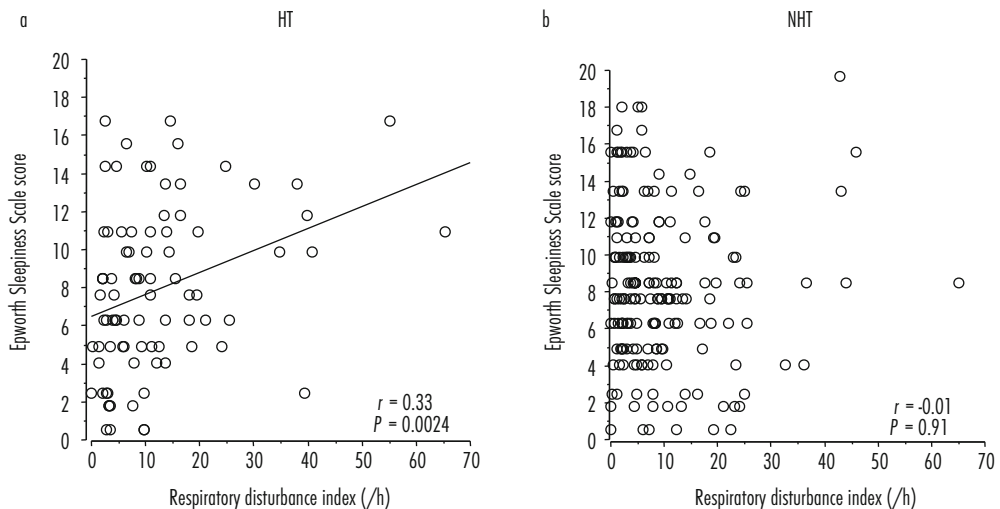
Figure 15.2. Relationship between Epworth Sleepiness Scale scores and respiratory disturbance index in the subjects with hypertension (HT) (a) and in the subjects without hypertension (NHT) (b) (Harada *et al.*, 2011).
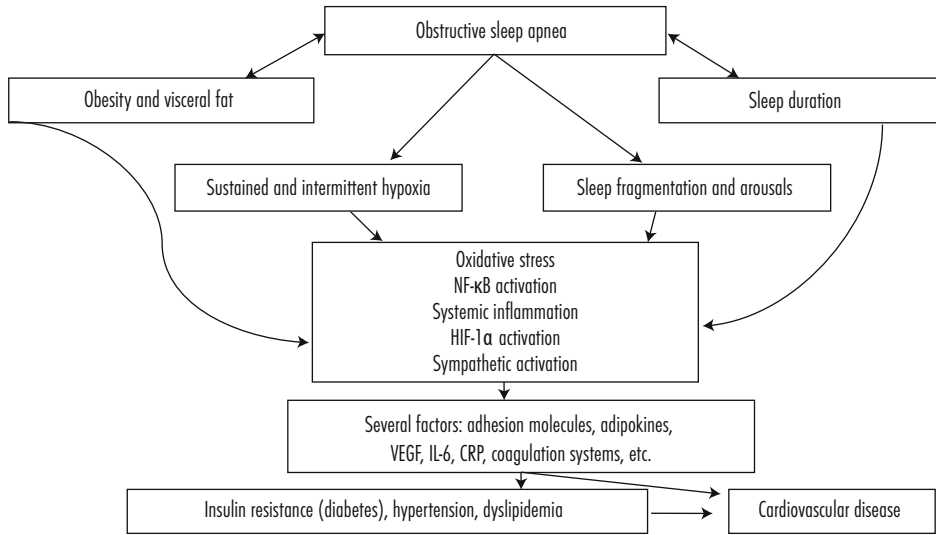
Figure 15.3. Schematic illustrating the pathogenetic mechanisms for the consequences of obstructive sleep apnea.

Acknowledgments

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Summary points

- The worldwide increase in the prevalence of obesity in the last several decades has been paralleled by a trend of reduced sleep duration.
- Experimental evidence suggests that short sleep duration is associated with an increase in the risk of obesity.
- Obstructive sleep apnea syndrome (OSAS) is one of the obesity-associated morbidities and obesity has become a significant risk factor in the pathophysiology of OSAS in children.
- OSAS may represent an important mechanism underlying the association between obesity and metabolic and cardiovascular morbidities.
- Although adenotonsillectomy remains the first line of treatment, evidence from recent years suggest that the outcomes of this surgical procedure may not be as favorable as expected, particularly in obese children.
- The association between sleep and obesity indicates that sleep may be one of the modifiable contributing factors to the obesity epidemic and that enhancing children's sleep may be an effective strategy for preventing and treating pediatric obesity.

16. Sleep and obesity in children

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Abstract

Over the past several decades, the prevalence of obesity in children and adolescents has grown to epidemic proportions. This obesity epidemic has been paralleled in modern society by a trend of reduced sleep duration that affects not only adults but also children and adolescents. Evidence has grown over the past decade supporting the role of short sleep duration as a novel risk factor for weight gain and obesity. Because the prevalence of short sleep duration is rapidly increasing in children, the association with obesity may have substantial effect on public health. The increase in both the prevalence of obesity and its severity has translated into a corresponding increase in the prevalence of obesity-associated morbidities, such as insulin resistance, type-2 diabetes mellitus, dyslipidemia, systemic hypertension, atherosclerosis, non alcoholic fatty liver, psychosocial complications and decreased quality of life, as well as obstructive sleep apnea syndrome (OSAS) and the obesity hypoventilation syndrome. The implications of OSAS in children, especially obese, are broad and sometimes complex. Given the precipitous rise in pediatric obesity and its associated risks, increasing attention has been paid to efforts to enhance prevention and treatment approaches. The association between sleep and obesity indicates that sleep may be one of the modifiable contributing factors to the obesity epidemic and that enhancing children's sleep may be an effective strategy for preventing and treating pediatric obesity.

Keywords: sleep disordered breathing, obstructive sleep apnea syndrome, sleep duration, obesity, leptin, ghrelin

Abbreviations

BMI	Body mass index
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
OSAS	Obstructive sleep apnea syndrome
PSG	Polysomnography
SDB	Sleep disordered breathing
T&A	Tonsillectomy & adenoidectomy

16.1 Introduction

The prevalence of obesity among children is continuously rising and has reached epidemic proportions worldwide. Data from the United Stated indicate that 32% of children and adolescents aged 2-19 years were considered overweight or obese in 2007-2008 (Ogden *et al.,* 2010). Concomitant with the increase in the prevalence of obesity, our society is facing a progressive reduction in sleep duration. Curtailment of sleep duration has become a widespread habit and a hallmark of modern society (National Sleep Foundation report 2006, 2008). This epidemic of chronic sleep deprivation affects not only adults but also children and adolescents.

Evidence has grown over the past decade supporting the role of short sleep duration as a novel risk factor for weight gain and obesity. It has been suggested that short sleep duration has a deleterious impact on glucose metabolism and appetite regulation. Because the prevalence of short sleep duration is rapidly increasing in children, the association with obesity may have substantial effect on public health.

The increase in both the prevalence of obesity and its severity has also translated into a corresponding increase in the prevalence of obesity-associated morbidities, such as type-2 diabetes mellitus and insulin resistance, dyslipidemia, systemic hypertension, atherosclerosis and ischemic heart disease, non alcoholic fatty liver/steatohepatitis, depression and decreased quality of life as well as OSAS and the obesity hypoventilation syndrome (Daniels *et al.,* 2005). Indeed, the classic presentation of children with OSAS as underweight children with adenotonsillar hypertrophy is being substantially replaced by more and more patients being overweight. Moreover, pediatric OSAS may represent an important mechanism underlying the association between obesity and metabolic and cardiovascular morbidities through potentiation of inflammatory cascades.

The association between sleep and obesity indicates that sleep may be one of the modifiable contributing factors to the obesity epidemic and that enhancing children's sleep may be an effective strategy for preventing and treating pediatric obesity.

This chapter reviews the multiple interactions between obesity, sleep duration, and sleep disordered breathing in children and adolescents.

16.2 Short sleep duration and obesity

Sleep plays an important role in energy balance. In rodents, food shortage or starvation results in decreased sleep, and conversely, total sleep deprivation leads to marked hyperphagia. Over the past 20-30 years, as rates of pediatric obesity have climbed, children's nocturnal sleep duration has declined (Dollman *et al.*, 2007). Data from the 2004 National Sleep Foundation's Sleep in America poll show that the mean sleep duration for school-aged children is 9.4 hrs per night (National Sleep Foundation report, 2004). These data are in contrast to the recommendations that children in this age group should obtain 10-11 hrs per night. In adolescents, data from the 2006 National Sleep Foundation's Sleep in America poll indicate that adolescents get 7-7.5 hrs of sleep on school nights and the amount of sleep varies by grade with adolescents tending to get less sleep as they get older (from 8.4 hrs for 6th grade to 6.9 hrs for 12th grade). Overall, 45% of adolescents get an insufficient amount of sleep on school nights (less than 8 hrs) (National Sleep Foundation report, 2006). Thus, children and adolescents do not achieve sufficient sleep length and it is not surprising that reports of fatigue and sleepiness, depressed mood and caffeine consumption are more frequent today than a few decades ago.

There have been 30 epidemiologic studies from 16 countries in recent years reporting on an inverse relationship between sleep duration and body weight in children and adolescents (Hart *et al.*, 2011). The majority of studies assessed the association between sleep duration and body weight through parent or self report and only two studies assessed sleep duration objectively through actigraphy. Measuring sleep duration with wrist actigraphy over a 24-hr period in 383 children aged 11-16, Gupta *et al.* (2002) reported one of the strongest associations between short sleep duration and obesity, with the odds of obesity increasing five-fold for every hr reduction in sleep duration. Benefice *et al.* (2004) using an accelerometer worn near the hip to assess sleep over 3-4 days in 40 Senegalese girls aged 13-14 years, observed that sleep duration was reduced by 6.85 min for every 1 kg/m^2 increase in BMI demonstrating a sleep-weight relationship in a non-obese population. Despite methodological differences, all epidemiological studies in children demonstrated negative associations between sleep duration and obesity risk (Hart *et al.*, 2011). Most studies found significant results even after controlling for potential confounders such as parental BMI and television viewing.

The longitudinal relationship between sleep duration and weight in children was examined in seven studies (Hart *et al.*, 2011). A study of over 8,000 children in the United Kingdom reported that sleep duration at the age of 30 months was associated with obesity at age 7 years after adjusting for maternal education, energy intake at 3 years of age, and sex (Reilly *et al.*, 2005). In a smaller cohort of 150 children it was also found that short sleep duration as reported by parents at the age of 3-5 years predicted overweight at the age of 9.5 years (Agras *et al.*, 2004). Those who became overweight had sleep duration about 30 minutes less than those who were normal weight at follow up.

The mechanism linking short sleep duration with weight gain is unknown, but there is growing evidence that the two key opposing hormones, leptin and ghrelin, are involved. In a

series of elegant laboratory studies, Spiegel and colleagues have shown that recurrent partial sleep restriction in healthy young adults induced marked alterations in glucose metabolism concomitant with decrease of the levels of the anorexigenic hormone leptin and increase in the levels of the orexigenic factor ghrelin. Importantly, these neuroendocrine abnormalities were correlated with increased hunger and appetite, which ultimately may lead to overeating and increased weight gain (Spiegel *et al.*, 2005). More recent experimental studies in adults have demonstrated increases in caloric intake from both snack foods and from main meals (Brondel *et al.*, 2010) when sleep is restricted, suggesting that less sleep may increase the risk of obesity via neuroendocrine changes that increase food intake. Short sleep duration has also been theorized to decrease energy expenditure by impacting non-exercise activity thermogenesis and by dropping core body temperature. No experimental studies involving the manipulation of sleep in children and weight related outcomes have been reported.

Another factor most likely involved in the interaction between sleep and obesity is the orexin system. Orexin A and B are two peptides synthesized by neurons which are concentrated in the lateral hypothalamus. Orexin containing neurons have a central role in both maintenance of arousal and energy balance. Increased orexin activity has been shown in animal models during periods of sleep deprivation. Thus, the orexin system may be the molecular link between wake-sleep regulation and the neuroendocrine control of appetite.

16.3 Obstructive sleep apnea syndrome

Pediatric OSAS has become widely recognized as a frequent disorder that is associated with substantial end-organ morbidities and increased health care utilization. During the past decade we have expanded our understanding on the mechanisms leading to obstructive sleep apnea, as well as those underlying the morbid consequences. Considering the potential interactions between OSAS and obesity, these secular changes in patient phenotype will most likely affect the frequency and severity of end-organ morbidities, particularly those involving the cardiovascular and metabolic systems.

OSAS in children is characterized by recurrent events of partial or complete upper airway obstruction during sleep, resulting in disruption of normal gas exchange (intermittent hypoxia and hypercapnia) and sleep fragmentation. The clinical spectrum of obstructive SDB includes OSAS, the upper airway resistance syndrome and at the low end of this spectrum, a condition that has been termed either primary or habitual snoring (i.e. habitual snoring in the absence of apneas, gas exchange abnormalities and/or disruption of sleep architecture).

The usual nighttime symptoms and signs of OSAS in children include snoring, noisy breathing, snorting episodes, paradoxical chest and abdominal motion, retractions, witnessed apnea, difficulty breathing, cyanosis, sweating and restless sleep. Daytime symptoms can include mouth breathing, difficulty waking up, moodiness, nasal obstruction, daytime sleepiness, hyperactivity, and cognitive problems.

SDB occurs in children of all ages, from neonates to adolescents. Snoring, the hallmark indicator of increased upper airway resistance during sleep, is a frequent symptom during childhood, being reported in up to 27% of children affected occasionally, and 7% to 12% reporting habitual snoring, that is, loud snoring recognized by parents 3 times or more per week (Urschitz *et al.*, 2004). The prevalence of OSAS is estimated at 2-3% of all children when using more stringent diagnostic criteria (Gislason and Benediktsdottir, 1995).

The pathophysiological mechanisms underlying the occurrence of OSAS are in many aspects quite different from those involved in adult OSAS. In the latter, OSAS is primarily, albeit not exclusively, associated with obesity, whereas the vast majority of cases of OSAS in children are due, at least to some extent, to enlarged tonsils and adenoids. The current understanding of OSAS in children and adolescents supports the existence of dynamic imbalance in upper airway function, whereby the combination of alterations in structural and anatomical characteristics, protective reflexes and neuromotor abnormalities of the upper airway are all implicated to a greater or lesser degree in any given particular child.

16.3.1 Obesity as a risk factor for pediatric OSAS

The epidemic increase in obesity seems to be leading to substantial changes in the anthropometric and demographic characteristics of children being referred for evaluation of OSAS. The classic presentation of children with OSAS as underweight children with adenotonsillar hypertrophy is being substantially replaced by an increasing proportion of young patients who are either overweight or obese (Gozal *et al.*, 2006).

Obese children are at increased risk for developing SDB and the degree of OSA is proportional to the degree of obesity (Arens and Muzamdar, 2010). In a case-control study design, Redline and colleagues (1999) examined risk factors for SDB in children aged 2-18 years, and found that the risk among obese children was increased 4-5 fold. In fact, for every increment in BMI by 1 kg/m^2 beyond the mean BMI for age and gender, the risk of OSAS increased by 12%. Similarly to non-obese children, several investigators have emphasized the role of adenotonsillar hypertrophy in obese children with OSAS (Arens and Muzamdar, 2010).

However, the requirement for adenotonsillar hyperplasia/hypertrophy is not always as prominent in the development of OSAS in obese children. In other words, intrinsic loading factors to the upper airway that are contributed by the presence of obesity appear to reduce the dependency on adenotonsillar hypertrophy in obese children with OSAS (Dayyat *et al.*, 2009). The interaction(s) between obesity and OSAS can be therefore explained by for example upper airway narrowing resulting from fatty infiltration of upper airway structures promoting pharyngeal collapsibility (Arens and Muzamdar, 2010). Indeed, the magnitude of adenotonsillar hypertrophy required for any given magnitude of OSAS severity was found to be smaller and Mallampati scores were found increased in obese children compared to non-obese children (Dayyat *et al.*, 2009) suggesting that soft-tissue changes and potentially fat deposition in the upper airway may play a significant role in the global differences in tonsillar and adenoidal size among obese and non-obese children

with OSAS. In addition, adiposity and central obesity reduce the intrathoracic volume and diaphragmatic descent during inspiration, particularly in the supine position, resulting in lower oxygen reserves and increased work of breathing during sleep (Arens and Muzamdar, 2010). Reduced lung volumes decrease airway stiffness by reducing the tracheal tethering effect and may further increase the risk of airway collapse and OSAS. Obesity could also result in blunted ventilatory responses to hypoxia and hypercapnia. Leptin, an adipocyte derived hormone regulating energy expenditure and food intake is readily found in the circulation, and its level appears to be determined by the degree of obesity. In addition, leptin appears to affect overall ventilatory drive, as well as influence peripheral chemoreceptor activity. Animal studies have demonstrated that hypoxia induces increases in both leptin gene expression and plasma leptin levels. Obesity is associated with peripheral and central leptin resistance, which in turn leads to relatively ineffective elevation of circulating leptin levels. Thus, reduced bioavailability of leptin resulting in altered ventilatory responses may also play a role in the interaction between obesity and OSAS (Shimura *et al.*, 2005).

In snoring children, both obesity and OSAS severity were found to contribute to the elevation in plasma leptin levels. Plasma leptin levels were found to be elevated in children with OSAS independent of obesity, and were significantly lower in those children with OSAS, but with minimal hypoxemia, when compared with children with OSAS and more pronounced hypoxemia (Tauman *et al.*, 2005). Thus, another possible explanation to the elevated plasma leptin levels observed in obesity and in OSAS is that leptin release provides an adaptive mechanism aiming to enhance ventilation in patients with respiratory depression subsequent to obesity, as well as in those with respiratory impairment due to OSAS. More research in children and adolescents is required to clarify these relationships.

16.3.2 Morbidities associated with OSAS: the role for obesity

While the clinical presentation of a child with OSAS is usually vague and requires increased awareness of the primary care physician, the implications of OSAS in children, especially obese, are broad and sometimes complex. If left untreated or alternatively if treated late, pediatric OSAS may lead to substantial morbidity that affects multiple target organs and systems. OSAS in children can lead to behavioral disturbances and learning deficits, cardiovascular morbidity, metabolic consequences, compromised somatic growth, as well as decreased quality of life and depression. In the current review we will focus on the cardiovascular and metabolic consequences of OSAS.

Cardiovascular consequences

The cardiovascular complications of OSAS are of immediate importance because earlier recognition could theoretically allow for formulation of interventional strategies, aiming to reverse this process in childhood and, thus, prevent its consequences later in adult life. Moreover, the present epidemic of obesity is likely to modify end-organ susceptibility to OSAS, particularly those involving the metabolic and cardiovascular system.

The recurrent episodes of upper airway obstruction that characterize OSAS lead to intermittent hypoxia, hypercapnia, and significant swings of intra-thoracic pressures, all of which may elicit disturbances in autonomic function. Using several methodological approaches such as heart rate variability analysis, electrocardiogram-derived spectral analyses, pulse transit time, and pulse arterial tonometry, studies have demonstrated autonomic nervous system dysfunction in children with OSAS (Montesano *et al.*, 2010; O'Brien and Gozal, 2005). Alterations in autonomic regulation are likely one of major underlying processes ultimately leading to systemic hypertension. Indeed, increased prevalence of systemic hypertension, alterations in blood pressure regulation, and changes in cardiac geometry have all been reported in children with OSAS (Amin *et al.*, 2008).

Recurrent hypoxic and hypercapneic episodes of OSAS elevate pulmonary vascular resistance leading to pulmonary hypertension. Similarly to adults, evidence of right ventricular dysfunction has been shown in children with OSAS (Shiomi *et al.*, 1993). Such elevations in pulmonary artery pressures may, potentially lead to *cor pulmonale*. In a recent report increased plasma levels of B-type natriuretic peptide, a marker of ventricular strain, have been found in children with OSAS with a decrease following adenotonsillectomy. Improvements in echocardiographic parameters of increased pulmonary pressure were also reported following adenotonsillectomy (Goldbart *et al.*, 2010).

Research from recent years indicates that pediatric OSAS constitutes a systemic low grade inflammatory condition. The induction of systemic inflammatory responses is most likely related to the generation of systemic oxidative stress secondary to the recurrent hypoxic and arousals episodes that characterize OSAS. Serum levels of high sensitivity C- reactive protein, an inflammatory protein produced in the liver, are a well-demonstrated predictive factor for cardiovascular morbidity, and may directly participate in atheromatous lesion formation. Increased circulating levels of C- reactive protein have been reported in children with OSAS, and can be reduced by effective treatment (Kheirandish-Gozal *et al.*, 2006; Tauman *et al.*, 2004). The reported alterations in autonomic nervous system and vasomotor tone, in combination with systemic inflammatory processes and atherogenesis associated with OSAS, are likely to induce functional disruption of the endothelium. Impaired endothelial function has been demonstrated in children with OSA with significant improvements 6 months after treatment with adenotonsillectomy (Gozal *et al.*, 2007). The long-term implications of endothelial and cardiovascular dysfunction in the context of pediatric OSAS remain unclear and completely unexplored, however it is likely that concurrence of OSAS, obesity, and high-risk genes during early childhood may activate processes ultimately leading to premature cardiovascular disease.

Since the prevalence of OSAS is higher in obese children, and since obesity constitutes one of the major risk factors for cardiovascular morbidity, it will be important to ensure that cardiovascular-related disease mechanisms thought to be secondary to obesity are not in fact a consequence of OSAS in obese individuals.

Metabolic consequences

The term 'metabolic syndrome', a known risk factor for cardiovascular disease in adults, refers to the clustering of insulin resistance, dyslipidemia, hypertension, and obesity. Insulin resistance and increased BMI during childhood emerge as the strongest predictors of the metabolic syndrome and cardiovascular morbidity and mortality in adulthood (Srinivasan *et al.*, 2002).

In adults, OSAS has been identified as an important risk factor for the metabolic syndrome. In children, insulin resistance appears to be primarily determined by the degree of obesity, and the contribution of OSAS is small (Gozal *et al.*, 2008; Tauman *et al.*, 2005). However, the concomitant presence of OSAS in obese children further amplifies the risk for lipid disturbances and insulin resistance (Gozal *et al.*, 2008; Waters *et al.*, 2007). Significant associations were observed between polysomnographic measures of OSAS and serum insulin/glucose ratios, LDL levels, HDL levels, LDL/HDL ratios, and apolipoprotein B serum concentrations. Effective resolution of OSAS resulted in significant reductions of LDL and apolipoprotein B and reciprocal increases in HDL in both obese and non-obese cohorts (Gozal *et al.*, 2008). In addition, insulin sensitivity improved in obese children when effective resolution of OSAS could be achieved. These findings suggest a pathogenic role of OSAS in lipid and glucose homeostasis, particularly considering that effective treatment of OSAS will result in marked improvements in metabolic control, independent of the degree of adiposity. In an older pediatric cohort, adolescents with OSAS were found to have a 6-fold increase in the odds of developing the metabolic syndrome compared to those without OSAS (Redline *et al.*, 2007).

End-organ metabolic injury, in the form of non-alcoholic steato-hepatitis, is potentially exacerbated in obese children by the concomitant presence of OSAS. Indeed, treatment of OSAS was associated with significant improvements in liver enzyme levels in the vast majority of patients with fatty liver disease (Kheirandish-Gozal *et al.*, 2008).

It is now well accepted that the physiological disturbances associated with obesity contribute to a chronic state of low-grade systemic inflammation, and that these derangements occur not only in adults, but are also discernible in children. The emergence of evidence associating obesity with inflammation has led to the identification of physiological mechanisms linking metabolically active tissue with systemic inflammation. White adipose tissue has been shown to produce over 50 molecules that have collectively been termed adipokines, and which play various functions involved in specific inflammatory and metabolic regulation. Among the several adipokines, leptin has emerged as an important adipokine that is not only modified by OSAS, but also plays an important role in the regulation of appetite, sleep, metabolic homeostasis, and respiratory control. Leptin stimulates production of pro-inflammatory cytokines including interleukin-6 and Tumor necrosis factor-α, both of which are independently induced by OSAS. Several studies indicate that OSAS leads to elevated circulating levels of leptin in adults and effective resolution of OSAS will reduce leptin levels particularly in adults who are non-obese. In children, elevations of circulating leptin levels, independent of the degree of obesity, have been reported (Tauman *et al.*, 2007), and a recent study (Kelly *et al.*, 2010) further confirmed these earlier observations.

16.4 Diagnosis

Since symptoms of OSAS are often subtle in children, a thorough history should be taken including detailed information on nighttime and daytime symptoms as well as OSAS associated morbidities such as neurobehavioral deficits, sleepiness, failure to thrive and systemic hypertension. The routine clinical evaluation of a snoring child is usually unlikely to demonstrate significant and obvious findings.

The accuracy of OSAS prediction based on history and physical examination is poor, even when the diagnostic interview is conducted by a sleep specialist. This relatively poor predictive ability has prompted the recognition and recommendation to refer symptomatic children to PSG evaluation to confirm or rule out the diagnosis of OSAS and to assess the degree of OSAS severity. The American Academy of Pediatrics has published a consensus statement outlining the requirements for pediatric PSG (Schechter, 2002).

16.5 Treatment

As mentioned above, OSAS in children is most commonly associated with adenotonsillar hypertrophy, even when obesity is present, such that the currently recommended initial treatment consists of surgical removal of the T&A (American Academy of Pediatrics, 2002). Evidence suggests that this intervention will lead to significant improvements in most cases, as recently reported from a meta-analysis (Brietzke and Gallagher, 2006; Friedman *et al.*, 2009).

Children with OSAS are at risk for respiratory compromise postoperatively, as a result of upper airway edema, increased secretions, respiratory depression secondary to analgesic and anesthetic agents, and post-obstructive relief pulmonary edema. A high risk of such complications is particularly encountered among children younger than 3 years of age, those with severe OSAS, and those with additional medical conditions such as obesity and craniofacial anomalies. These patients should not undergo outpatient surgery, and cardiorespiratory monitoring should be performed for at least 24 hrs postoperatively to ensure their stability (Gerber *et al.*, 1996; Rosen *et al.*, 1994).

Postoperative PSG evaluation 8-12 weeks after surgery is recommended for children who continue to snore, children with pre-operative severe OSAS and children with additional risk factors such as obesity and craniofacial anomalies in order to ensure that additional interventions are not required (American Academy of Pediatrics, 2002).

In recent years, it has become apparent that the outcomes of T&A may not be as favorable as expected, particularly when OSAS is severe pre-operatively or when obesity is present. Indeed, the frequency of residual OSAS after T&A is estimated at 45-50% after surgery (Bhattacharjee *et al.*, 2010). These findings have promoted a debate as to whether overnight sleep studies should routinely be conducted after T&A.

Continuous positive airway pressure or bilevel positive airway pressure is considered the second line of treatment in children with unresolved OSAS after T&A. Although this intervention appears to be safe in children, the extensive behavioral conditioning needed to achieve adequate adherence in children precludes widespread implementation of this intervention. Nevertheless, several published studies have shown a beneficial response to continuous positive airway pressure /bilevel positive airway pressure in children, as well as favorable adherence rates (Marcus *et al.*, 2006).

For overweight and obese children, weight loss should also lead to improvement in number and severity of apneic episodes. In adults, the beneficial effects of weight reduction programs on OSAS are so well recognized that this intervention constitutes one of the principal recommendations for management of OSAS in adults. Although adenotonsillectomy should remain the primary approach for OSAS in obese children, every effort should be made to achieve significant weight reduction in these children. Indeed, resolution of sleep apnea after weight loss in five morbidly obese children has been reported (Willi *et al.*, 1998), such that in special cases in whom surgery is not a viable option, intensive weight management may be particularly beneficial. Intensive weight reduction program is an important first line step towards a more definitive treatment for obese children with or without OSAS. Of note, weight loss improves not only the severity of sleep-disordered breathing, but that of other complications of childhood obesity and OSAS, such as vascular dysfunction (Ng *et al.*, 2004).

16.6 Obesity hypoventilation syndrome

This syndrome, also known as Pickwickian syndrome, is defined as a combination of obesity and awake arterial hypercapnia ($PaCO_2$>45 mm Hg) in the absence of other known causes of hypoventilation. There are only a few reports of children with obesity hypoventilation syndrome (Ward and Marcus, 1996). However with the recent increases in the prevalence of obesity in children and adolescents, this condition is likely to become increasingly frequent.

Patients with obesity hypoventilation syndrome will present, similar to OSAS, with excessive daytime sleepiness, fatigue, and/or morning headaches. However, the presence of daytime hypercapnia and hypoxemia may lead to polycythemia, pulmonary hypertension, and to right ventricular failure. Decreased ventilatory responses to hypercapnia and hypoxia are usually found during waking and during sleep, in contrast to pediatric patients with straightforward OSAS, who generally will have normal respiratory drive (Marcus *et al.*, 1994). In addition, decreased nocturnal alveolar ventilation, with or without obstructive sleep apnea/hypopnea events will be present.

In children with obesity-hypoventilation syndrome and OSAS, removal of the tonsils and adenoids was recommended as the initial therapeutic procedure (Ward and Marcus, 1996). The reversibility of the blunted hypercapnic responsiveness following T&A in some of these children suggests that a component of the blunted response may be secondary to the mechanical effects

of obesity on the respiratory system rather than a primary abnormality in neurological control of breathing. Since depressed ventilatory drive may occur in patients with significant hypoxia and hypercapnia in the immediate postoperative period following removal of tonsils and adenoids, mechanical ventilatory support may be required at least in the early postoperative period. For most of the patients however, T&A will not be sufficient to complete resolve the problem, and BIPAP by nasal mask is necessary.

It should be emphasized that weight loss is the optimal and most efficient treatment for obesity-associated hypoventilation. Indeed, weight loss will reverse daytime hypercapnia and improve blood gases and lung volumes (Rapoport *et al.*, 1986).

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Diseases and conditions associated with altered sleep

Summary points

- Diabetes mellitus indirectly influences sleep via its complications.
- Complications (acute or chronic) can occur earlier in the course of the disease due to non-adherence to diet, medication, lifestyle, etc.
- Nocturnal hypoglycaemia is the most important acute complication with an impact on sleep, although it does not necessarily awake the patients.
- The symptoms of chronic complications such as heart failure or polyneuropathy impact on sleep e.g. by nycturia or pain.
- There is a more than coincidental overlap of diabetes mellitus with conditions at least favoured by diabetes such as obstructive sleep apnoea syndrome (OSAS), central sleep apnoea (CSA) syndrome, restless legs syndrome (RLS) and depression that also disturb sleep.

17. Sleep in diabetic patients: a focus on acute and chronic complications of diabetes mellitus affecting sleep

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Abstract

In diabetes mellitus adherence to dietary measures is a cornerstone of therapy. Incompliance can favour acute or chronic complications impacting on the sleep of diabetic patients. Nocturnal hypoglycaemia is the most important acute complication affecting sleep, although it does not necessarily awake the patient. Effects of hypoglycaemia on sleep architecture and sleep quality are reported. Nycturia is one symptom of chronic hyperglycaemia obviously able to disturb sleep. It also occurs as a symptom of heart failure and its diuretic therapy, also a chronic complication of diabetes. Diabetic neuropathy is a further chronic complication with high prevalence in diabetic patients. It affects sleep in its manifestation as painful peripheral neuropathy. Mechanisms not completely understood associate diabetic neuropathy with central sleep apnoea, with the obstructive sleep apnoea syndrome and the restless legs syndrome, all impairing sleep architecture and sleep quality. Depression and diabetes promote each other via several mechanisms. Depression disturbs the circadian rhythm and sleep. Frequently used medications of diabetic patients such as antihypertensive or lipid-lowering drugs can also interfere with sleep.

Keywords: hypoglycaemia, neuropathy, restless legs syndrome, nycturia, comedication

Abbreviations

ACE	Angiotensin converting enzyme
AHI	Apnoea hypopnoea index
AN	Autonomic neuropathy
CAI	Central apnoea index
CGM	Continuous glucose monitoring
CSA	Central sleep apnoea
OSAS	Obstructive sleep apnoea syndrome
PAT	Peripheral arterial tonometry
PPDP	Painful peripheral diabetic neuropathy
PSQI	Pittsburg sleep quality index
REM	Rapid eye movement
RLS	Restless leg syndrome

17.1 Introduction

Diet is an indirect factor contributing to interferences between sleep and diabetes mellitus. Chronic incompliance with the dietetic restrictions may worsen the natural course of the disorder and lead to an earlier onset and more pronounced 'late' complications of the disease affecting sleep such as painful neuropathy, sleep apnoea, or nycturia due to heart failure or to chronic hyperglycaemia. Non-adherence to dietetical measures may also lead to more 'acute' complications such as hypoglycaemia (in combination with insulin or insulinotrophic drugs), able to disrupt sleep severely.

In patients with diabetes mellitus sleep disturbances are reported more frequently than the general population. This has been well established in type 2 diabetic patients. Baseline data from 1,002 diabetic patients (total number of participants n=4,872) who took part in the Sleep Heart Health Study revealed differences in the respiratory disturbance index, the sleep time with O_2 saturation <90% and periodic breathing. Furthermore, the diabetic participants had spent more time in sleep stages 1 and 2, less time in deeper sleep stages (3, 4, rapid eye movement). With the level of obesity an important confounder, the authors also hypothesised that sleep disturbances might in part also result from dysfunction of the autonomic nervous system (Resnick *et al.*, 2003).

The observation of a higher amount of sleep disturbances has more recently been confirmed in patients with type-1 diabetes too (Van Dijk *et al.*, 2011): in 99 patients with long-standing diabetes (26.9±1.2 yrs), 35% reported subjective poor sleep quality (vs. 20% matched, non-diabetic controls). The authors reported an association with peripheral polyneuropathy, habitual snoring, higher depression scoring and nocturnal hypoglycaemia. They failed to demonstrate an association with the HbA1c levels. Van Dijk *et al.* had used the PSQI to assess subjective sleep quality.

As can be seen from these reports, several factors may impact on sleep in diabetic patients (Figure 17.1, Table 17.1). Among the best characterised is the association between diabetes mellitus and the OSAS. Since this will be addressed in another chapter of this book, the review will focus on the other points listed in Table 17.1.

17.2 Acute complications: hypoglycaemia during sleep

Nocturnal hypoglycaemia was reported in the literature as a condition mainly observed in type 1 diabetic patients and as the consequence of an imbalance between the insulin dose and the content, amount and timing of meals as well as factors such as physical activity and alcohol consumption. With the novel method of CGM, several study groups demonstrated not only a surprisingly high incidence of nocturnal hypoglycaemic events in type 1 diabetic patients, but also in type 2 diabetic patients under insulin therapy (Boland *et al.,* 2001; Weber *et al.,* 2007).

Depression
(disturbed circadian rhythm)

Obstructive sleep apnoea
(cardiovascular risk)

Insulin resistance
(cardiovascular risk)

Hypoglycaemia
(shock)

Neuropathy
(collapse)

Nycturia
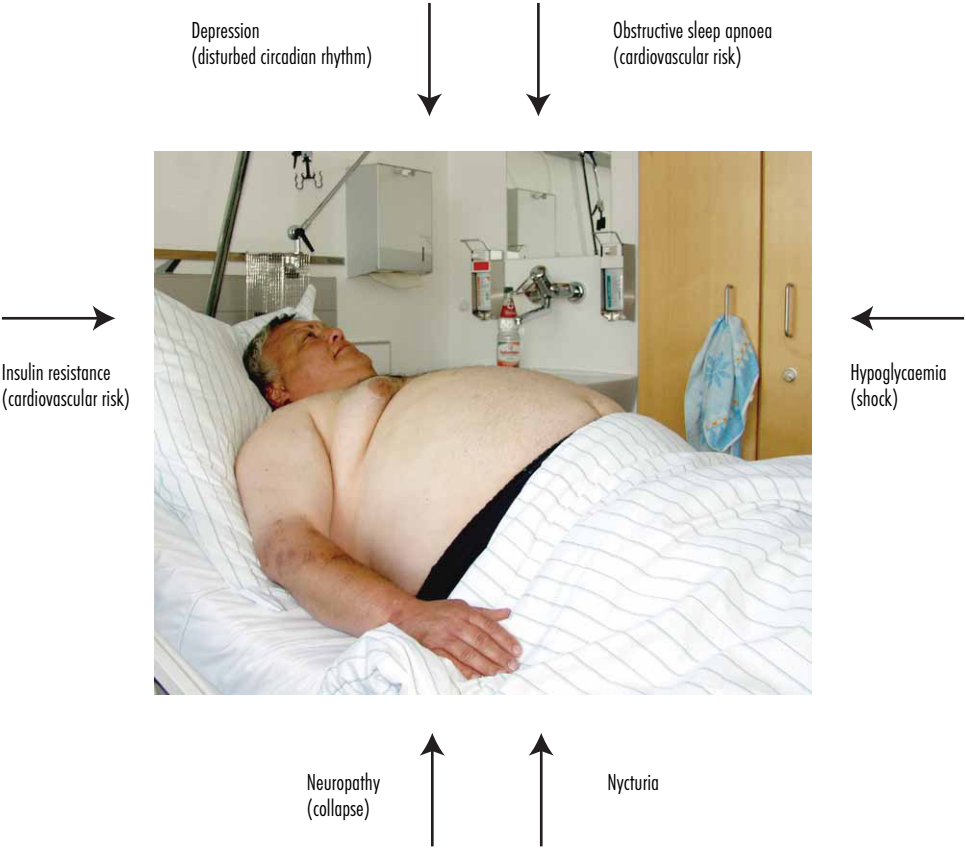
Figure 17.1. The disturbed and 'dangerous' sleep of a diabetic patient. Factors interfering with the sleep of a diabetic patient and in part elevating cardiovascular risk.

Table 17.1. Acute and chronic complications of diabetes responsible for sleep disturbance.

	Reasons	Possible symptoms having an impact on sleep
Acute	hypoglycaemia	shock
	hyperglycaemia	nycturia
Chronic	polyneuropathy	pain
		impaired thermoregulation
	coronary heart disease/	pain
	heart failure	nycturia
		dyspnoea
	sleep apnoea (central, obstructive)	poor sleep quality
		daytime sleepiness
	restless legs syndrome	poor sleep quality
	depression	circadian rhythm disturbance
	comedication:	diverse
	ACE inhibitors	
	beta-blockers	
	sartans	
	calcium channel blockers	
	statins	

Several studies reported the most nocturnal hypoglycaemic episodes during late sleep (between 3 and 7 am) (Bendtson, 1995).

However, these episodes are asymptomatic in many cases and do not necessarily cause an awakening of the patients. In diabetic patients, the glycogen response against hypoglycaemia is lost early in the course of the disease. This is why the counterregulatory response is typically a sympathoadrenal one.

In an experimental setting with stepwise nocturnal reduction of the plasma glucose towards 50 mg/dl (2.8 mmol/l), a blunted response of epinephrine and norepinephrine was demonstrated (eight adolescent type 1 diabetic patients vs. six matched controls). Interestingly, the same effect could be observed in the healthy controls, indicative, that the state of sleep is the reason and not e.g. autonomic neuropathy in diabetic patients. In the study, all participants underwent polysomnography during the procedure, nobody had awakened during the hypoglycaemic episodes. A general reduction of sympathetic activity occurs during sleep stages 3 and 4. Unfortunately, these are stages of deep sleep predominating the first third of the sleep cycle, which is the time the patients are most prone to severe hypoglycaemia.

The finding, that the nocturnal sympathoadrenal response to hypoglycaemia is blunted in diabetic patients was confirmed in several studies. To further characterise the response of sleeping diabetic patients to hypoglycaemia, less invasive techniques such as CGM and PAT were used. The principle is, that digital arteries are primarily innervated by alpha-adrenergic receptors, thus, reflecting the activity of the sympathetic system. Using PAT and CGM, Pillar *et al.* (2003) detected nocturnal hypoglycaemia in five of 15 children with type-1 diabetes. These events were associated with an increased percentage of the slow wave sleep stages 3 and 4, and with a trend toward increased total sleep time, decreased sleep latency and increased sleep efficiency (Pillar *et al.,* 2003). The association with increased slow wave sleep during hypoglycaemic episodes was also observed in other studies (Matyka *et al.,* 2000). Natural sleep was an advantage of this study, PAT and heart rate measures did not reveal increased sympathetic activation during the hypoglycaemias. Spontaneous awakening did not differ compared to a control group.

Jauch-Chara and co-workers investigated the response to nocturnal hypoglycaemia with respect to the different sleep stages (in the before described studies, the events were typically induced by insulin infusion or reported during early sleep) (Jauch-Chara *et al.,* 2007). In 16 healthy subjects, hypoglycaemia (2.2 mmol/l) was induced immediately after onset of sleep and after 3.5 hrs of sleep in another night. The pattern of awakening caused by hypoglycaemia was similar, the hormonal response was weaker during late sleep. Given, that these findings do also account for diabetic patients, this could be a reason for the clinically observed accumulation of critical hypoglycaemic events in the later part of night.

Although the most episodes of nocturnal hypoglycaemia are reported to be asymptomatic, it is a well known finding for the diabetologist, that some patients complain of sleep disturbances (vivid dreams or nightmares), morning headache, chronic fatigue, or mood changes (mainly depressive), likely to be the consequence of repetitive nocturnal hypoglycaemia. Furthermore, these observations shall not lead to the misunderstanding that awakening, or at least disturbed sleep as a response to hypoglycaemia, is an extremely rare event.

Schultes *et al.* (2007) tried to characterise the nature of this 'awakening signal' that provoked the awakening from sleep in 16 adult type 1 diabetic patients and controls without clinical evidence of autonomic neuropathy. The setting was one night with hypoglycaemia induced by insulin infusion (a target nadir of 2.2 mmol/l was reached after about 60 minutes). Only one patient did awake at 2.7 mmol/l (vs. all 10 controls at values 2.2-2.7 mmol/l) and had a strong counterregulatory hormonal response. The authors detected a temporal pattern with an increase in epinephrine 7.5±1.6 min before polysomnografic signs of wakefulness in the persons that awoke. They speculated, that awakening by hypoglycaemia is part of a central nervous system response launched in parallel with hormonal counterregulation.

As a rule of thumb, a fast fall in glucose concentration seems to be a more effective signal in causing counterregulatory response than a slow decline in glucose levels (Pillar *et al.,* 2003, Schultes *et al.,* 2007).

Although not topic of this book, the mechanisms, by which the body spontaneously – and frequently without symptoms such as sleep disturbance – restores normoglycaemia after a nocturnal hypoglycaemic event seem poorly understood. Glucagon-release during hypoglycaemias is impaired early after onset of diabetes mellitus. Adrenal stimulation and arousals are obviously not the sole mechanisms, as demonstrated in the above mentioned studies.

The most of the above described studies were experimental settings with insulin-induced hypoglycaemic events. This shall not lead to the misunderstanding, that insulin is the only possible culprit in causing these events. Several oral antidiabetic drugs used in the therapy of type 2 diabetic patients have an insulinotrophic mode of action and are capable to induce (also nocturnal) hypoglycaemias as well. Oral antidiabetic drugs and their hypoglycaemic potential are listed in Table 17.2.

There is no hint that hyperinsulinaemia – a rather typical metabolic phenomenon in type 2 diabetic patients – has substantial effects on sleep (Kern *et al.,* 1996).

17.3 Acute and chronic complications: nycturia

Some fields for research are that obvious that they do not offer an exciting or commendable approach for scientific studies. There is no doubt that nycturia is a factor severely disturbing sleep. In diabetic patients, nycturia can either be caused by glycaemic values above the renal threshold of 160-180 mg/dl (8.9-10 mmol/l). Another possibility – especially in elderly type 2 diabetic patients – is heart failure or its therapy with diuretic drugs. For example, in a sample of 733 adults with type-2 diabetes studied from 1991-1994 (Third National Health and Nutrition Examination Survey), 40.7% of the patients had a HbA1c value ≥8%, corresponding with a mean glucose value ≥180 mg/dl (Harris, 2000). These disappointing numbers make it likely, that a high percentage of diabetic patients suffer from sleep disturbance due to nycturia.

Table 17.2. Oral antidiabetic drugs and their potential to cause hypoglycaemia. The non-susceptible drugs can be used in combination with insulin or sulfonylureas and thus also contribute to hypoglycaemic events.

Drug class	Drugs	Hypoglycaemic potential
Sulfonylureas	glimepiride, glipizide, glyburide (= glibenclamid)	high
Meglitinides	repaglinide, nateglinide	high
Biguanides	metformin	none
Alpha glucosidase inhibitors	acarbose, miglitol	none
Thiazolidinediones	pioglitazone, rosiglitazone	none
Dipeptidyl peptidase inhibitors (DPP IV inhibitors)	sitagliptin, vildagliptin, saxagliptin, linagliptin	none

The number of patients with heart failure as a possible reason for nycturia is also high in type 2 diabetic patients: of 5,464 community-dwelling adults ≥65 years old in the Cardiovascular Health Study without baseline heart failure, 862 had DM. Incident heart failure occurred in 31% of the participants with diabetes mellitus during ≥13 years of follow-up (Roy *et al.,* 2011).

17.4 Chronic complications: neuropathic pain

It goes without saying, that pain is an important disruptor of sleep. A common 'late' complication of diabetes mellitus is peripheral neuropathy which occurs in 30-50% of the patients (Veyes *et al.,* 2008). PPDP is estimated to be present in 10-20% of the patients with diabetes (Veyes *et al.,* 2008). PPDP may be a discomfort with burning, aching or tingling character. Unfortunately, the pain increases progressively during the day, worsens at night and, thus, significantly impairs sleep quality (Odrcich *et al.,* 2006). It is not surprising, that pain was identified as a main predictor of sleep disruption in diabetes next to nycturia (Lamond *et al.,* 2000).

The Medical Outcomes Study Sleep measure is a well-evaluated and common tool to evaluate sleep quality (Viala-Danten *et al.,* 2008). It is a 12-item measure divided into 6 dimensions evaluating: sleep disturbance, snoring, sleep awakening short of breath or with headache, sleep adequacy, somnolence and quantity of sleep/optimal sleep. Using the Medical Outcomes Study Sleep Measure in 255 diabetic patients with PPDP (age 61±12.8 years), Zelman *et al.* (2006) demonstrated that PPDP is associated with considerable sleep impairment with less sleep quality not only compared to the general population (n=1,011), but also to patients with other chronical diseases (n=3,445) and even with postherpetic neuralgia (n=89) (Zelman *et al.,* 2006).

Since PPDP varies between individuals concerning character, intensity and expression, this may be the reason, why no studies with homogenous groups are available to characterise the effect of PPDP on the different sleep stages in a polysomnography lab.

17.5 Chronic complications: autonomic neuropathy and central sleep apnoea

Neuropathy in patients with diabetes mellitus might be a factor to predispose these patients to sleep apnoea. A damage to the nervous system may affect central respiratory drive and predispose them for CSA. Apart from the important factor of obesity, neuropathy of the upper airway dilator muscles may impair their nocturnal tonus and eventually result in the upper airway collapse typical for OSAS.

Surprisingly, CSA is only poorly investigated in patients with diabetes mellitus. Among the first to study the impact of autonomic neuropathy in diabetic patients was Guilleminault *et al.* (1981). In a small study of 4 type 1 diabetic patients, the authors detected obstructive sleep apnoeas in two and central sleep apnoeas in one of the patients (Guilleminault *et al.,* 1981).

In 1985, 19 patients with diabetes (12 type 1, seven type 2) underwent nocturnal polygraphic monitoring. Five of the type 1 group had breathing patterns of central or obstructive sleep apnoea, only one type 2 diabetic patient had moderate OSAS. The authors demonstrated a clear relationship between the presence of neuropathy and sleep-related breathing abnormalities (Mondini and Guilleminault, 1985). Bottini and coworkers have investigated the occurrence of sleep-disordered-breathing in (non-obese) diabetic patients. 18 had autonomic neuropathy, 8 patients had no signs of AN (Bottini *et al.,* 2003). All of them underwent overnight polysomnography. An AHI≥10 was reported in 5 of the subjects with AN and in none of the patients without AN. All events detected were obstructive, no periodic breathing or central sleep apnoeas were observed. As can be seen, such studies included only small patient samples and the role and incidence of CSA in diabetes is still far from clear: In the Sleep Heart Health Study (Resnick *et al.,* 2003), the CAI was determined in the diabetic participants at risk for cardio vascular disease (n=470). CAI is defined as 3 or more apnoeas without respiratory effort per hour of sleep. After multiple statistical adjustments, the authors reported no statistical significance of diabetes in relation to CAI. However, the patients were not especially investigated for neuropathy, the number of patients concerned low and the percentage of CAI was low between 4.7 (≥2 events/h) and 2.5 (≥4 events/h). In a sample of 40 Japanese diabetic patients the prevalence of CSA (defined as 5 or more events/h) was surprisingly high with 32.3%. The finding, that these patients had a higher intima-media thickness suggests, that these patients had already long-standing diabetes and a high prevalence of AN can be presumed (Kashine *et al.,* 2010).

17.6 Chronic complications: overlap with the OSA syndrome and with depression

OSAS is a disorder characterised by a repetitive nocturnal collapse of the upper airway. This results in apnoeas (defined as a cessation of breathing for at least 10 s), causing hypoxia, exaggerated negative intrathoracic pressure and a burst of sympathetic activity ('arousal') that terminates the apnoeas. The sleeping patient is unaware of the arousals, but sleep architecture is disturbed and daytime sleepiness is a common symptom. Obesity and insulin resistance are typical features of OSAS, as well as type-2 diabetes. A surprisingly high number of patients with diabetes has an AHI≥15, one formal criterium for OSAS. In a study conducted by the author with a screening device in 498 patients with diabetes type 2 and 58 patients with diabetes type 1, 37.4% of the patients had an AHI≥15 suggestive of OSAS and 34.9% had an AHI between 5 and 14 (Schober *et al.,* 2011), see Figure 17.2. Einhorn *et al.* (2007) published their investigations from research with 279 American patients with known type-2 diabetes and found an overall prevalence of 36% at an AHI cutoff value of ≥15 events/hr in patients with a mean BMI of 33.5 kg/m^2 (Einhorn *et al.,* 2007).

It is not clear whether there is a causality between OSAS and diabetes mellitus, but at least both disorders seem to promote each other. There is meanwhile a wide body of literature dealing with the interferences between the two conditions that is addressed in Chapter 20 of this book.

AHI in the subgroups <5 / 5-14 / ≥15
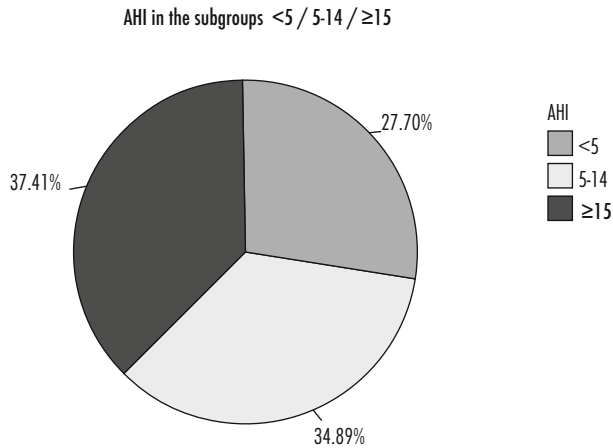
Figure 17.2. Prevalence of sleep apnoea in diabetic patients. In a study conducted by the author with a screening device in 498 patients with diabetes type 2 and 58 patients with diabetes type 1, 37.4% of the patients had an apnoea hypopnoea index (AHI) ≥15 suggestive of obstructive sleep apnoea syndrome (OSAS) and 34.9% had an AHI between 5 and 14. The mean duration of diabetes was 16.9 yrs in the type 1 diabetic group and 8.3 yrs in the type 2 diabetic group (Schober *et al.,* 2011).

The same observation accounts for depressive disorders. Both conditions seem to promote each other. One typical feature of depression is a disturbance of the circadian rhythm and sleep (van Steenbergen-Weijenburg *et al.,* 2011). Mechanisms of interaction between depression and diabetes mellitus are given in Figure 17.3.

17.7 Chronic complications: overlap with the restless legs syndrome

RLS is increasingly diagnosed in diabetic patients. Three times more patients with RLS report having diabetes than the general population. Although the etiology of RLS is poorly understood and the association between RLS and diabetes is not thoroughly studied, a relation to diabetic neuropathy seems possible. In the most recent case-control study between patients with type-2 diabetes with RLS (n=18) and diabetes without RLS (n=21) using different self-rating scales (PSQI, Epworth sleepiness scale etc.) the first group reported a significant difference in the quality of sleep, sleep latency, sleep efficiency and daytime dysfunction (Cuellar and Ratcliffe, 2008).

17.8 Concomitant medication

Type-2 diabetes is a condition typically accompanied by other disorders such as obesity, hypertension and dyslipidaemia ('Metabolic Syndrome'). Thus, a type 2 diabetic patient (and several type 1 diabetic patients) are also treated with antihypertensive and lipid-lowering drugs,
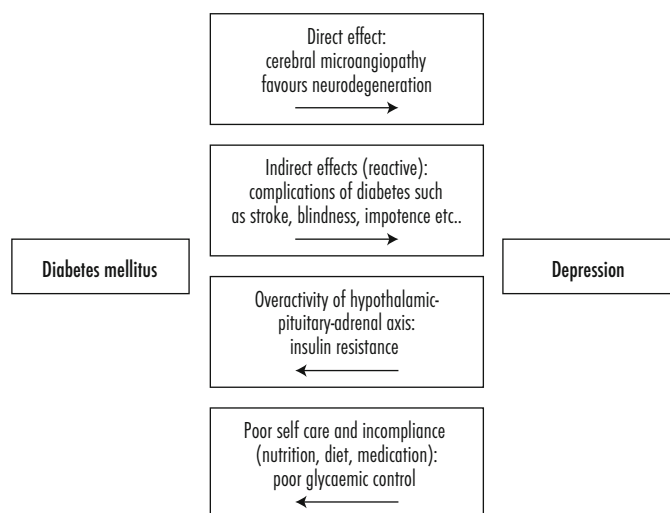
Figure 17.3. Interactions between diabetes mellitus and depression.

both capable to interact with the sleep cycle. Almost all classes of antihypertensive drugs have been investigated concerning their impact on sleep.

Calcium channel blockers were reported in 186 patients with hypertension and OSAS to be associated with shorter sleep duration (-41 min; P=0.005) (Nerbass $et\ al.,$ 2011).

Beta-blockers are reported to have different effects: 22 patients treated with nebivolol for 6 weeks reported an improved sleep quality (PSQI), whereas sleep quality worsened in 17 metoprolol-treated patients (Yilmaz $et\ al.,$ 2008). Since Beta-blockers affect norepinephrine neuroreceptors, they are the antihypertensives most likely to induce nightmares (Kastalli $et\ al.,$ 2006).

ACE inhibitors such as enalapril are discussed to promote OSA. Since the therapy increases the availability of bradykinin, this might contribute to upper airway inflammation and promote upper airway collapse, particularly in people who develop upper airway symptoms during therapy with ACE inhibitors (Cicolin $et\ al.,$ 2006).

There is hardly any literature about the use of sartans and sleep quality. Recently, a case report was published describing an association between valsartan intake and the occurrence of nightmares (Kastalli $et\ al.,$ 2006). A resume of these interactions with sleep is given in Table 17.3.

Statins are the most commonly used lipid-lowering drugs in patients with diabetes mellitus. The reports are contradictory. Among the first reports was a parallel-group study between lovastatin and pravastatin (n=12). Lovastatin significantly increased the wake time after sleep onset and stage 1 sleep, pravastatin was not associated with sleep disturbance (Vgontzas $et\ al.$, 1991).

Table 17.3. Antihypertensive drugs frequently used in diabetic patients: effects on sleep. The drug class is given in bold letters. Note that these effects are described in small patient samples, sometimes only case reports.

	Sleep quality	Possible effect
Calcium channel blockers		
amlodipine, lacidipine, diltiazen, verapamil	–	shorter sleep duration
Beta blockers		(in general: higher frequency of nightmares)
nebivolol	+	unknown
metoprolol	–	unknown
ACE inhibitors		
enalapril	–	promotes OSAS (?)
Sartans		
valsartan	–	nightmares (case report)

OSAS = obstructive sleep apnoea syndrome. +: improved; –: negative effect.

These findings could not be reproduced in 16 subjects that underwent a randomised, double-blind, three-way crossover therapy with lovastatin, pravastatin and placebo. No statistical differences were determined for the following sleep parameters: total sleep time, total awake time, wake time after sleep onset, efficiency of sleep, percentage of different sleep phases (Ehrenberg *et al.,* 1999).

A 4 week study in 24 males with equivocal doses of simvastatin and pravastatin provided no evidence for differences relevant to insomnia between pravastatin, simvastatin and placebo. The sole finding was a higher number of entries to stage 1 sleep after simvastatin treatment, whereas the latency to stage 1 sleep was significantly prolonged in the pravastatin group (Eckernäs *et al.,* 1993).

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Summary points

- The prevalence of type-2 diabetes within the population is high and is growing.
- There is a strong epidemiological link between sleep disturbances (quality and quantity) and risk factors for type-2 diabetes and cardiovascular disease and it is imperative that the potential population and public health implications are assessed.
- Both quantity and quality of sleep are associated with an increased risk of type-2 diabetes and should be regarded as a behavioural risk factor for its development.
- These risk factors are in part determined by the environment, it is possible that they are amenable to modification through both education and counselling.
- Favourable modifications of physical and working environments may also help to promote sufficient sleep and avoid habitual and sustained sleep deprivation and disruption.
- Intervention studies are required to determine if sleep extension or sleep improvement can have beneficial effects.

18. Sleep quantity and quality and the risk of type-2 diabetes

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Abstract

The aim of this chapter is to review the data, which describes the relationship between sleep disturbance of quantity and quality and the incidence of type-2 diabetes. Firstly the relationship with sleep quantity is described and then with sleep quality (difficulty in initiating sleep and difficulty in maintaining sleep). The review clearly demonstrates that both quantity and quality of sleep consistently and significantly predict the risk of the development of type-2 diabetes. The potential mechanisms that might underlie these associations are considered. Finally, the public health importance of this data is considered with possible health recommendations.

Keywords: sleep quality, sleep quantity, type-2 diabetes

Abbreviations

BMI	Body-mass index
CI	Confidence interval
OSA	Obstructive sleep apnoea
RR	Relative risk

18.1 Introduction

A large variety of social, cultural, psychological and pathophysiological factors can have an effect on sleep and can affect both its quantity and quality. Modern societal changes, including the 24-7 availability of commodities, longer working hours and extended shift-work patterns have led to population-wide curtailment of sleep duration across westernized populations (Akerstedt and Nilsson, 2003). An associated increase in tiredness and deleterious effects on a variety of metabolic, endocrine and immune systems have been reported (Broussard and Knutson, 2010; Miller and Cappuccio, 2010). Furthermore, acute short-term, laboratory and cross-sectional observational studies indicate that disturbed or reduced sleep is associated with glucose intolerance, insulin resistance, reduced acute insulin response to glucose and a reduction in the disposition index (Spiegel *et al.,* 2009), thus predisposing individuals to type-2 diabetes. The question as to whether longer term effects of sustained sleep deprivation have effects on glucose and insulin metabolism, and hence on the predisposition to type-2 diabetes, has been addressed in a number of prospective population-based studies (Ayas *et al.,* 2003; Beihl *et al.,* 2009; Björkelund *et al.,* 2005; Gangwisch *et al.,* 2007; Hayashino *et al.,* 2007; Kawakami *et al.,* 2004; Mallon *et al.,* 2005; Nilsson *et al.,* 2004; Yaggi *et al.,* 2006). Sleep duration has also been associated with components of the metabolic syndrome (Katano *et al.,* 2011). There are, however, large variations between these studies including variations in population size, duration of follow up, etc. The evidence from such studies was therefore examined in more detail in a large meta-analysis of 13 independent cohorts (Cappuccio *et al.,* 2010), some of the findings from which are discussed in more detail below.

18.2 Sleep quantity and type-2 diabetes

The meta-analysis is composed of studies including over 100,000 participants and more than 3,000 incident cases of type-2 diabetes (Cappuccio *et al.,* 2010). The search criteria included any potential studies from 1955 to 2009. Only prospective studies were included in the analysis and follow up needed to be for at least 3 years. In general, duration of sleep was assessed by self-reported habitual sleep duration using questionnaires, except in one study where duration was obtained by direct interview. Short sleep was defined in most studies as 5 or 6 hrs/night but in one study it was defined as 7 hrs/night (see review for more details Cappuccio *et al.,* 2010). Long sleep was defined as either 8 or 9 hrs/night (see review for details). When results were reported for men and women separately, they were entered into the analyses as separate cohorts. The

assessed outcome was incident cases of type-2 diabetes. Methods to ascertain new cases of type-2 diabetes varied among studies: in five studies, questionnaires were used; in five other studies more direct diagnostic criteria were used (see review for more details (Cappuccio *et al.*, 2010)). In this meta-analysis a random effects model was used to determine the pooled RR of developing type-2 diabetes for both sleep quantity and sleep quality. The heterogeneity among the studies and possible publication bias were also determined using standard methods (see Cappuccio *et al.*, 2010 for details). The summary of the findings are given in Table 18.1.

18.2.1 Short duration of sleep

The study indicates that short duration of sleep is associated with a greater risk of developing type-2 diabetes. Whilst there was no evidence of publication bias there was evidence of statistical heterogeneity among studies. For short duration of sleep (≤5-to-6 hrs/night) the RR was 1.28; 95% CI 1.03 to 1.60; *P*=0.024. The observed effect in men (RR 2.07 [95% CI 1.16-3.72]) tended to be larger than that in women (1.07 [0.90-1.28], heterogeneity test *P*=0.04).

18.2.2 Long duration of sleep

For long duration of sleep the study demonstrated no evidence of publication bias or heterogeneity (Table 18.1). Long sleep (>8-to-9 hrs/night) is associated with a greater risk of type-2 diabetes (RR 1.48 [1.13 to 1.96; *P*=0.005]).

Table 18.1. Quantity and quality of sleep and the risk of developing type-2 diabetes (Cappuccio *et al.*, 2010).

Exposure & outcome	No of participants	No of events	Relative risk (95% CI)	Combined effect (*P*)	Heterogeneity[1]	Publication bias
Short sleep & type-2 diabetes	90,623	3,079	1.28 (1.03-1.60)	0.024	I^2=58% (11 to 80) Q= 18.9; *P*=0.015	Eggers test *P*=0.14
Long sleep & type-2 diabetes	88,611	2,903	1.48 (1.13-1.96)	0.005	I^2=37% (0 to 74) Q=9.6; *P*=0.14	Eggers test *P*=0.42
Difficulty in initiating sleep & type-2 diabetes	24,192	787	1.57 (1.25-1.97)	<0.0001	I^2=0% (0 to 75) Q=4.37; *P*=0.50	Eggers test *P*=0.37
Difficulty in maintaining sleep & type-2 diabetes	18,213	544	1.84 (1.39-2.43)	<0.0001	I^2=22% (0 to66) Q=6.38; *P*=0.27	Eggers test *P*=0.15

[1] Heterogeneity was tested by Q statistics and quantified by I^2 and H statistics (Higgins and Thompson, 2002). CI = confidence interval.

18.3 Sleep quality and type-2 diabetes

In these studies, sleep quality was assessed as difficulty in initiating or maintaining sleep, by questionnaire.

18.3.1 Difficulty in initiating sleep

A significant increased risk was observed for difficulty in initiating sleep (1.57 [1.25 to 1.97; *P*<0.0001]). Furthermore, as shown in Table 18.1, the study did not find any evidence of publication bias and there was no heterogeneity amongst the different studies.

18.3.2 Difficulty in maintaining sleep

Sleep maintenance reflects sleep consolidation and was associated with an increase in risk (1.84 [1.39 to 2.43; *P*<0.0001]). Once more this meta-analysis showed no publication bias and findings were consistent across the studies (Table 18.1).

Further analyses performed in this study demonstrated that the effects were, by and large, comparable in men and women, and did not depend on the type of assessment of exposure and outcome nor on the variation in the definitions of short or long sleep. Furthermore, a large number of potential confounders, particularly age and BMI, were considered in the primary analyses and it was observed that the size of the effect tended to increase with the duration of follow-up. The study is useful in that for the first time it is possible to see a quantitative estimate of the size of sleep quantity and quality on the risk of developing type-2 diabetes. The risk varies between 28% in people who habitually sleep less than 5-6 hrs/night and 84% in those people who have difficulty maintaining their sleep. These findings indicate that sleep has an important effect of potential public health importance. It is necessary therefore to understand the likely mechanisms underlying these effects as this may aid in the prevention of these deleterious effects.

18.4 Potential mechanisms

Sleep disturbances may be related to the development of type-2 diabetes via a number of different mechanisms. These include changes in appetite, caloric intake and energy expenditure (Knutson *et al.,* 2009; Spiegel *et al.,* 2009) and impaired glycaemic control (Spiegel *et al.,* 2005). Short term sleep deprivation studies indicate that sleep restriction may lead to a decrease in leptin, an appetite suppressant hormone and an increase in ghrelin, an appetite promoting hormone (Spiegel *et al.,* 2004). It is postulated that the changes in these hormones could lead, with time, to an increase in appetite and an increased in BMI and associated disorders such as type-2 diabetes. Others have indicated that sleep deprivation leads to an increase in blood glucose levels (Thomas *et al.,* 2000) and an increase in evening cortisol levels (Spiegel *et al.,* 1999) leading to reduced insulin sensitivity the following morning and an increase in blood glucose (Van Cauter *et al.,*

1997). Sleep deprivation may also lead to an increase in sympathetic nervous activity and a reduction of insulin secretion from pancreatic beta-cells (Stamatakis and Punjabi, 2010).

OSA, which is the most common sleep disorder, is characterized by the complete or partial collapse of the pharyngeal airway during sleep, which leads to hypoxia. To resume ventilation, feedback mechanisms arouse the individual, which leads to sleep disruption. Longitudinal studies have indicated that snoring, which is an accepted marker of OSA, is associated with changes in glucose metabolism. A limitation of many such studies, however, is that polysomnography, the accepted gold standard for the diagnosis of OSA, has not been used (Al-Delaimy *et al.,* 2002; Grunstein *et al.,* 1995). Support for a causal link between OSA and glucose metabolism is obtained from studies that have demonstrated that continuous positive airway pressure treatment for OSA has beneficial effects on glucose metabolism (Brooks *et al.,* 1994; Harsch *et al.,* 2004). Other studies have indicated that OSA may be associated with adverse changes in the sympathetic nervous system and the hypothalamic-pituitary-adrenal-axis (Miller and Cappuccio, 2010). Furthermore, it has been suggested that OSA may contribute to the development of not just diabetes but also metabolic syndrome, which is the term used to describe the clustering of insulin resistance, obesity, hypertension and an adverse lipid profile in individuals. It is suspected that the chronic intermittent hypoxia and sleep loss in OSA may affect many biochemical pathways and in particular, may contribute to an increase in and/or maintenance of chronic inflammation (Tasali and Ip, 2008).

Emerging evidence also suggests that disruption of the light-dark cycle and melatonin levels may contribute to the development of metabolic syndrome, type-2 diabetes and insulin resistance (Hardeland *et al.,* 2011).

18.5 Implications

The findings from the recent meta-analysis indicate that the association between sleep quantity and quality and type-2 diabetes is relatively consistent in different populations (Cappuccio *et al.,* 2010). Furthermore, they indicate an effect size of potential public health relevance. The limitations of this analysis however do need to be considered. Firstly, the quality of the findings is dependent on the quality of the individual studies included. Secondly, such a meta-analysis of observational data cannot directly control for confounding. Thirdly, whilst there was no evidence of publication bias the results can only be representative of the studies that have been included. Nevertheless, the strength and consistency of these findings are important and should be used as a guide for the definition of future research strategies and public health policy decisions. Moreover, sleep should be considered as an important modifiable factor for the prevention of type-2 diabetes. Further research is required to understand the potential underlying mechanisms and to determine if it is possible, for example by extending sleeping times, to modify the measured attributable risk.

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Summary points

- Obstructive sleep apnea (OSA) is characterized by snoring, pauses in breathing and fragmentation of sleep.
- OSA is highly linked with metabolic and cardiovascular diseases.
- Obesity is the most important risk factor for OSA.
- OSA has the tendency to progress over a varying period of time, particularly in the case of weight gain and lack of effective treatment.
- Lifestyle intervention with weight loss has been found to be an effective treatment in treating patients with mild-severe OSA.
- Weight reduction also improves the other obesity related disturbances of the cardiometabolic syndrome.

19. Obstructive sleep apnea: diet and lifestyle treatments

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Abstract

Sleep disorders have become a public health concern in the modern society, affecting millions of people. Although, obstructive sleep apnea (OSA) is one of the most recognized sleep disorders, the majority of OSA still remain undiagnosed. Obesity is the most important risk factor for OSA and in fact, vast majority of OSA patients are obese. OSA as such, has been linked with increased cardiovascular morbidity and mortality, and OSA patients often display the cardiometabolic syndrome. The exact underlying mechanisms behind these associations are complex and not fully understood. In obese individuals, weight reduction and increased physical activity form the cornerstones for the prevention and treatment of cardiometabolic syndrome, and recent controlled intervention trials strongly suggest that weight reduction together with a healthy diet and increased physical activity may correct or at least improve the symptoms of OSA. However, regardless of promising results in terms of symptoms of OSA and the undoubted cardiometabolic benefits of changing lifestyles, weight reduction as a treatment of OSA is still underrated by many clinicians. Based on current knowledge, clinicians should review their previous attitudes, even suspicions about weight reduction as an effective treatment for OSA patients. Nevertheless, we do also need large well-controlled trials on the effects of different weight reduction programs among OSA patients to determine the overall efficacy of different treatment modalities and their long-term success.

Keywords: sleep disordered breathing, weight loss, physical activity, cardiometabolic syndrome

Abbreviations

AHI	Apnea-hypopnoea index
BMI	Body mass index
CPAP	Continuous positive airway pressure
OSA	Obstructive sleep apnea
VLCD	Very low calorie diet

19.1 Introduction

Obesity has become a serious public health concern in recent decades, leading to increased morbidity and mortality, in particular from cardiovascular diseases (Lavie *et al.,* 2009). Obesity is also the most important risk factor for OSA and in fact, most OSA patients are obese (Young *et al.,* 2004). The co-existence of obesity and OSA has complex and a far more serious impact on the cardiovascular and metabolic consequences than either of these conditions on their own. OSA as such, has been found to have an independent association with cardiovascular diseases, type-2 diabetes, cardiometabolic syndrome, deterioration of an individual's quality of life and working capacity, and increased mortality (Peppard *et al.,* 2000; Punjabi *et al.,* 2009; Tuomilehto *et al.,* 2008; Young *et al.,* 2002). The importance and the effectiveness of weight loss in treating OSA have been well-known for more than two decades. The majority of the earlier studies on weight reduction in OSA patients evaluated either the effects of low and very low calorie diet programs in moderately overweight patients or the effects of bariatric surgery upon weight and concurrent OSA in severely obese patients (Dixon *et al.,* 2005; Greenburg *et al.,* 2009; Kajaste *et al.,* 1994, 2004; Kansanen *et al.,* 1998; Schwartz *et al.,* 1991; Smith *et al.,* 1985). These studies have lead to conclusions that weight loss could reduce the severity of OSA, but that it was not a curative treatment for most patients. However, although weight reduction is recommended in all clinical guidelines, until recently there has been a lack of well-executed randomized intervention studies on the effect of weight reduction upon OSA. In the first randomized study to be conducted, we demonstrated that a lifestyle intervention lasting one year including an early weight reduction program represented a feasible and curative treatment for the vast majority of overweight patients with mild OSA (Tuomilehto *et al.,* 2009). These findings have been supported by two other recent randomized studies, one examining obese OSA patients with type-2 diabetes and the other in obese patients with severe OSA, including an observational follow-up phase Foster *et al.,* 2009; Johansson *et al.,* 2009, 2011). Most importantly, although the results of these and earlier studies are encouraging, it is not known, whether these favourable changes can be sustained after the discontinuation of the intervention. The recent post-interventional follow-up of our randomized study demonstrated that a successful weight reduction with lifestyle intervention can maintain the improvements of OSA for at least one year after the actual termination of the intervention (Tuomilehto *et al.,* 2010). Virtually no attention has been paid earlier to the weight reduction as a potential key treatment modality not only for OSA but also for related co-morbidities. Recently this topic has finally attracted attention because of well-designed intervention trials, which unequivocally highlight the potential of weight reduction in this condition. It should be noted

that weight reduction, more physical activity and adopting a healthy diet and lifestyle habits may have a marked influence on the well-being and cardiovascular risk of the OSA patients due their beneficial effects on many cardiovascular and metabolic risk factors, e.g. glucose metabolism. The aim of this chapter is to focus on the new information on the importance of weight loss in the treatment of OSA and its metabolic co-morbidities in overweight patients.

19.2 Epidemiology of obesity and obstructive sleep apnea

Excess body weight is perhaps the greatest of health burden throughout the world, affecting almost every aspect of life and representing a major challenge to medical practice. It has been estimated that globally 1.6 billion adults are overweight (BMI>25 kg/m^2) and 400 million are obese (BMI>30). In the USA, one out of every three adults is categorized as being obese. In Europe, the trends are going in the same direction, for example in Finland one out of every five adults has BMI>30. Overall, it has been estimated that 20% of individuals in western societies are obese and 1-2 % are morbidly obese (BMI>40). The increasing prevalence of morbid obesity is particularly worrying, and in the future this group of patients has been predicted to increase most rapidly. Furthermore, it has been suggested that life expectancy for adults may decrease in the future due to the obesity epidemic. In the USA, health care costs are already over 30% higher for obese individuals as compared to those with a normal BMI. In Europe, obesity is estimated to be responsible for 2-8% of health costs and 10-13% of deaths (Withrow *et al.,* 2010).

OSA is one of the most common sleep disturbances, affecting mostly the middle-aged work force. The prevalence of OSA without excessive daytime sleepiness is 24% in men and 9% in women aged 30-60 years. OSA with excessive daytime somnolence (OSAS) occurs in 2-4% of the adult population between the ages of 30 and 60 years. Adding together that the patients are frequently unaware of the associated symptoms that are often identified either by a bed partner or family member and the definite lack of necessary sleep medicine training of health care professionals in most medical specialties, it may be well-justified to assume that a great number of patients still remain undiagnosed (Young *et al.,* 2002).

19.3 Pathophysiology and risk factors of obstructive sleep apnea

OSA occurs when there are repetitive collapses of the upper airway during sleep causing an obstruction of breathing, reduction in airflow and oxygenation. For patients with OSA, these disturbed nocturnal breathing functions also result in recurrent arousals causing a significant fragmentation of their sleep. The pathophysiology of OSA is complex and most likely multifactorial, consisting of a combination of predisposing anatomical factors and impaired neuromuscular compensatory responses. However, overweight is considered as the most important risk factor for OSA, BMI>29 increases the risk for OSA by 10-fold. It has been estimated that 60-90% of all patients with OSA are obese (Pillar and Shehadeh, 2008). Furthermore, there is current evidence that systemic inflammatory mediators related to obesity and central adiposity may have additional

effects also in pharyngeal neural and mechanical control mechanisms that mediate collapsibility and increase OSA susceptibility. The other major predisposing factors for OSA are male gender, age and certain anatomical factors e.g. large tonsils, prominent uvula, mandibular micrognathia and nasal deformities (Young *et al.,* 2002). Due to all these factors, the airspace of the naso-, and oropharynx decreases and there is a narrowing of the upper airways, thus increasing the risk of OSA in the supine position and a loss of neuromuscular compensation at the onset of sleep. Furthermore, it has recently been demonstrated that deviations in craniofacial morphology are much more common in normal weight than in overweight adult patients with OSA (Pahkala *et al.,* 2011). Together these findings imply that there may be two different phenotypes of OSA; one related to excess fat tissue and the other to craniofacial abnormalities.

19.4 Clinical symptoms related to obstructive sleep apnea

OSA is characterized by loud snoring, pauses in breathing, and sleep fragmentation. Due to the sleep fragmentation, OSA is often accompanied by daytime symptoms; fatigue, lack of concentration, morning headache, impotence, deterioration of an individual's quality of life and working capacity (Young *et al.,* 2002). The breathing pauses can be divided into apneas and hypopneas; there is a total obstruction of air flow during apnea, whereas in hypopnea, the airflow is decreased to the extent that it causes oxygen desaturation. The severity of OSA is classified based on the AHI, describing the episodes of apnea or hypopnea per hour of sleep. This is measured by either in-laboratory polysomnography or at-home cardio-respiratory recording. According to the AHI-index, sleep apnea can be divided into mild (5-15), moderate (15-30) and severe (over 30) disease (American Academy of Sleep Medicine Task Force, 1999).

19.5 Obesity related pathophysiology of obstructive sleep apnea

The association between obesity and OSA seems to be bi-directional; obesity itself increases the risk for OSA, but, on the other hand, OSA may also predispose the individual to weight gain (Pillar and Shehadeh, 2008). It has been postulated that obesity leads to narrowing of the upper airway structure, alteration in its function (such as collapsibility), reduced chest wall compliance, disturbances in the relationship between respiratory drive and load compensation, reductions in functional residual capacity and hypoxemia, and also hormonal changes. Furthermore, it has been claimed that obesity has other influences on sleep disordered breathing due to an exacerbation of intermittent hypoxia related to the excessive body weight. Sleep fragmentation, typically associated with OSA, on the other hand, is associated with decreased leptin levels and increased ghrelin levels, and therefore, with an increase of hunger and appetite. Weight gain increases the possibility for the development of OSA in previously healthy people, and accelerates the progression of earlier diagnosed OSA, particularly in patients who are already overweight. Furthermore, it has been reported that it is more difficult to improve OSA by weight reduction than to develop or further deteriorate OSA by more weight gain (Pillar and Shehadeh, 2008; Young *et al.,* 2002). This finding clearly highlights the importance of maintaining normal body

weight by providing general information to the public via prevention programs or in the case of individuals who are overweight, committing them to early control of their condition and more active treatment of their obesity.

19.6 Weight reduction in obstructive sleep apnea

The importance and the effectiveness of weight loss in treating OSA have been recognized for more than 25 years (Smith *et al.,* 1985). The majority of the weight reduction and OSA studies have evaluated either the effects of low and VLCD programs in moderately overweight patients with OSA or the effects of bariatric surgery upon weight and concurrent OSA in severely obese patients. Overall, the average weight loss and improvement in AHI after dietary interventions have been around 3-18% and 3-62%, respectively. After bariatric surgery, the average weight reduction has been in the range of 12-37% with the improvement in AHI being 48-90%. All of the studies have revealed the strong association between the extent of weight loss and the improvement in nocturnal respiratory functions (Table 19.1). Similar results have also been found in studies evaluating the effects of pharmacological agents on weight loss and OSA. However, pharmacotherapy is recommended to include concomitant lifestyle changes and the selection of drugs is still limited.

Although the effect of weight reduction on OSA has been encouraging, the trials have been criticized for many reasons, e.g. lack of control groups, non-randomized study design, lack of long-term follow-up and too small sample sizes to provide solid evidence for the clinical practice guidelines on the benefits of weight loss in OSA. Moreover, many studies have been conducted with small selected subgroups, e.g. severely obese patients usually with severe or at least heterogeneous severity of OSA. Based on above mentioned facts, the previous studies examining the effect of weight loss as a treatment of OSA have led to conclusions that weight loss may reduce the severity of OSA, but that it is not a curative treatment option for most patients.

Accumulating and improving knowledge of weight loss programs has demonstrated that if they are to be successful, additional changes in lifestyles in conjunction with energy restriction per se, are essential. This can be achieved by supervised intervention and regular visits to a clinical nutritionist, who can provide dietary and lifestyle counselling at each visit emphasizing the quality of diet, increased exercise, and modification of lifestyles in general, especially eating behavior. This kind of intervention through lifestyle changes has already been successfully used in the prevention of type-2 diabetes (Lindström *et al.,* 2006), and also in larger scale in the implementation programs for prevention of type-2 diabetes in clinical settings. The goal of lifestyle interventions is to reduce the body weight by at least 5-10% and has mostly focused on patients with mean BMI less than 35.

In the first randomized study conducted by our group, we demonstrated that a lifestyle intervention lasting one year including an early weight reduction program with a VLCD was a feasible and curative treatment for the vast majority of overweight patients with mild OSA

Table 19.1. Randomized controlled studies (A) and major selected non-randomized studies (B) on the effects of weight reduction on obstructive sleep apnea.

Study	Country	Design	Method	Subjects (n)	Follow-up (months)	Weight loss in kg (% from baseline)	AHI (% from baseline)
Johansson *et al.*, 2011	Sweden	B	VLCD + lifestyle	63	12	12 (9)	-17 (16)
Tuomilehto *et al.*, 2010	Finland	A	VLCD + lifestyle	82	24	8 (8)	-5 (46)
Johansson *et al.*, 2009	Sweden	A	VLCD	63	2	20 (18)	-23 (62)
Foster *et al.*, 2009	USA	A	VLCD + lifestyle	264	12	11 (11)	-10 (42)
Barnes *et al.*, 2009	Australia	B	VLCD + lifestyle	12	12	8 (8)	-6 (26)
Kajaste *et al.*, 2004	Finland	A	VLCD + CB	31	24	(9)	-19 (37)
Kansanen *et al.*, 1998	Finland	B	VLCD	18	3	9 (8)	-12 (39)
Kajaste *et al.*, 1994	Finland	B	CB	26	24	5 (4)	-1 (3)
Schwartz *et al.*, 1991	USA	B	diet	15	16	7 (17)	-51 (61)
Smith *et al.*, 1985	Australia	B	diet	15	5	10 (9)	-26 (47)
Lettieri *et al.*, 2008	USA	B	bariatric surgery	24	12	54 (37)	-23 (49)
Dixon *et al.*, 2005	Australia	B	bariatric surgery	24	18	45 (29)	-48 (78)
Sugerman *et al.*, 1992	USA	B	bariatric surgery	20	12	56 (33)	-31 (48)
Charuzi *et al.*, 1992	Israel	B	bariatric surgery	47	10	18 (12)	-54 (90)[a]

AHI = apnea-hypopnea index; VLCD = very low calorie diet; CB = cognitive-behavioral; [a]Apnea index.

(Tuomilehto *et al.*, 2009). These findings were supported by another recent randomized study of obese OSA patients with type-2 diabetes (Foster *et al.*, 2009). A third randomized study in moderate-severe OSA patients with CPAP recently demonstrated that an adjuvant weight loss program significantly improved OSA compared to CPAP (Johansson *et al.*, 2009). This study noted that weight reduction programs may have an important role also for patients with more severe OSA. Furthermore, the observational 12-month follow-up of the study revealed that 48% of the patients with originally severe OSA no longer required CPAP and one out of every ten patients experienced total remission of the disease (Johansson *et al.*, 2011). Therefore, despite the earlier beliefs that lifestyle changes may not be long-lasting when treating patients with OSA, these results indicate that these arguments may not be tenable. A recent 2-year follow-up study demonstrated that favorable changes achieved by supervised lifestyle intervention could be sustained for at least one year after the discontinuation of the intervention (Tuomilehto *et al.*, 2010). Thus, our earlier findings and those of another randomized study have highlighted that lifestyle intervention with weight reduction could achieve in a significant relief of partial and complete obstructions by reducing both hypopnea, and especially apnea indices. This could well explain the stability of achieved improvements in respiration during sleep (Foster *et al.*, 2009;

Tuomilehto *et al.,* 2009). The improvement of OSA was clearly correlated with the changes in body weight (Figure 19.1). However, it has been suggested that in patients with OSA, less than 50% of the overall response to weight loss may be attributed to reductions in passive mechanical properties with the remainder to concomitant improvements in neuromuscular control of upper airways. This kind of effect could be seen in the 2-year follow-up of our lifestyle intervention study, which demonstrated that although there was a typical regaining of the weight lost achieved by the lifestyle intervention, the nocturnal respiratory function remained improved and did not follow the trend of modest weight gain (Figure 19.2). This all supports our proposal that a weight reduction program with lifestyle counseling should be part of the routine treatment for all OSA patients and represent the first-line treatment in the early phases of the disease (i.e. mild OSA) when associated with overweight. When the disease is at an early stage it is most likely that the organ systems may still have the capacity to fully recover from its adverse impact or at least, the progression of the disease may be prevented (Tuomilehto *et al.,* 2009, 2010).

Based on current knowledge of the evolution of OSA, we believe that weight gain poses a high risk for further progression of the disease towards more severe disease, particularly in those patients who already have partial obstruction of their upper airways (because of anatomical or functional causes) with mild to moderate OSA (Berger *et al.,* 2009). A similar approach to that used in two diabetes prevention studies with lifestyle interventions could be relevant also for OSA
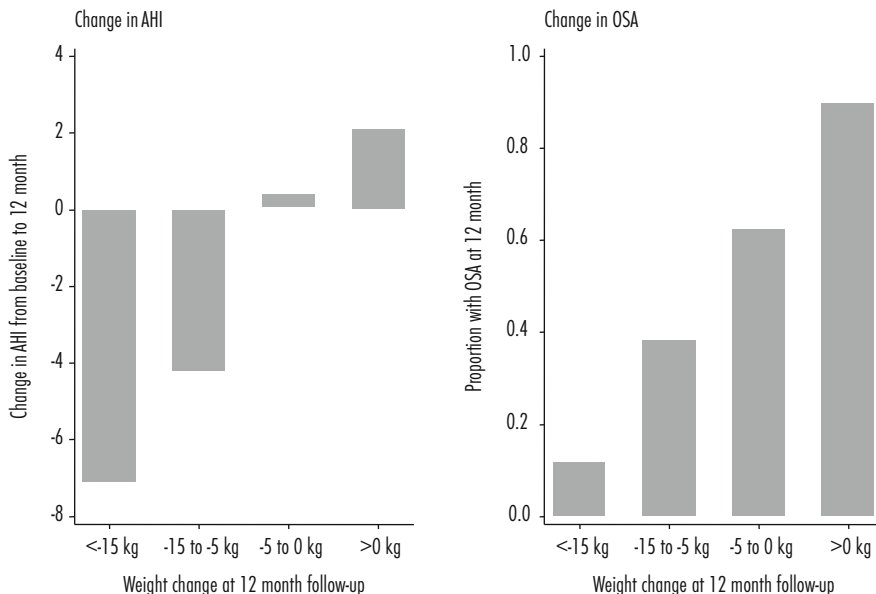
Figure 19.1. Changes in apnea-hypopnea index (AHI) in relation to changes in body weight, and the proportion of patients (%) with obstructive sleep apnea (OSA) (AHI>5) in relation to the weight change categories <-15 kg, -15 to -5 kg, -5 to 0 kg, and >0 kg after a 12-month lifestyle intervention program (Tuomilehto *et al.,* 2009, reprinted with permission of the American Thoracic Society. Copyright by American Thoracic Society)
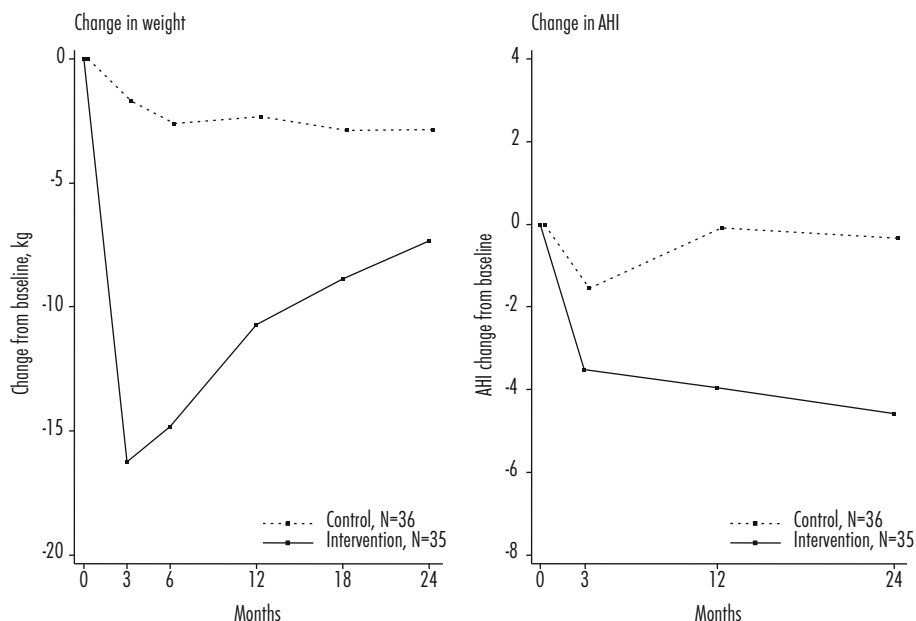
Figure 19.2. The mean changes in weight and apnea-hypopnoea index (AHI) over the whole 24-month follow-up period according to the measurements at the baseline, 3, 12 and 24 months. Vertical bars indicate 95% confidence intervals (Tuomilehto *et al.*, 2010, reprinted with permission of the American Society for Nutrition. Copyright by American Society for Nutrition).

patients with mild symptoms in order to interrupt its progression and thus, to prevent increased morbidity and mortality. In the more severe OSA cases with obesity, we propose a more aggressive weight reduction, and a VLCD may form a part of this program, if applicable. Moreover, one cannot overestimate the importance of regular physical activity as a component of the lifestyle intervention. Previously the association between regular exercise and reduced likelihood of sleep disordered breathing and type-2 diabetes has been well-characterized. Therefore, we also emphasize the importance of lifestyle modification in general, which includes a healthy diet and increased physical activity. As for the prevention of diabetes, these programs have been shown to be cost-effective, as well (Li *et al.*, 2010).

Besides these cornerstones of a successful lifestyle intervention i.e. healthy diet and regular exercise, one has to keep in mind also other factors that may predispose to sleep disordered breathing and at its worst to OSA. Sedative drugs, alcohol and smoking have been suggested as possible risk factors for OSA. In fact, recently our study group demonstrated that impaired nasal breathing and smoking may prevent the beneficial effects of weight reduction in the treatment of overweight patients with OSA (Blomster *et al.*, 2011). Therefore, the assessment of nasal breathing and educational guidance for smoking should always be included in the management of OSA patients.

It is commonly claimed that weight loss may not be sufficient when treating patients with OSA, but the recent randomized studies have demonstrated that a more aggressive treatment of obesity in OSA patients is well-founded. Although lifestyle intervention is the cornerstone of weight loss treatment, it is particularly alarming that there is an exploding prevalence of morbid obesity, in fact this patient group has been predicted to increase most rapidly. Not surprisingly, conventional lifestyle and weight reduction programs have proven to be ineffective over the long-term in these patients. The co-morbidities associated with obesity have generated a search for new modalities of treatments. Bariatric surgery has increased worldwide as many benefits have been associated with this procedure and currently, over 200,000 operations are being performed in the USA each year. In many European countries, the demand for obesity surgery is also rapidly increasing. The current clinical guidelines for surgical treatment of obesity are BMI≥40 or BMI≥35 with obesity-related co-morbidity, and prior unsuccessful attempts with conventional weight reduction programs (Buchwald and Oien, 2009). Bariatric surgery seems to be highly effective in the treatment of OSA in morbidly obese patients since it achieves improvements in sleep disordered breathing and symptoms related to OSA. According to a meta-analysis, the mean percentage of excess weight loss was 61% resulting in a significant resolution of all obesity related co-morbidities, particularly of OSA, which improved in 86% of patients (Buchwald *et al.,* 2004). Furthermore, in those severely obese patients already using or in the need for additional CPAP treatment, the weight loss achieved by bariatric surgery ameliorated nocturnal breathing function and resulted in a reduction of the airway pressure needed for successful CPAP treatment, thus perhaps improving compliance with the treatment.

19.7 Cardiometabolic syndrome and obstructive sleep apnea

Cardiometabolic syndrome is a cluster of risk factors, which alone or in different combinations increase the risk for type-2 diabetes, cardiovascular morbidity and mortality. A recent study also suggested that sleep disturbance co-aggregated with other components of the cardiometabolic syndrome and could be the second most important determinant after obesity (Nock *et al.,* 2009). There are several reports that OSA is also associated with the cardiometabolic syndrome and type-2 diabetes (Lévy *et al.,* 2009; Tuomilehto *et al.,* 2008; Young *et al.,* 2002). In clinical work, the association between type-2 diabetes, cardiometabolic syndrome and OSA should be kept firmly in mind. There is accumulating evidence that obesity, cardiometabolic syndrome and OSA are major risk factors in the development of cardiovascular diseases; what is needed are better clinical tools and guidelines to achieve early diagnosis and improved treatment in certain risk groups, such as obese patients. The interactions between OSA, type-2 diabetes and cardiometabolic syndrome are complex and multifactorial, but they do seem to be highly influenced by common feature obesity, particular central obesity. Often these conditions are present in the same individual and it has been proposed that the coexistence of these conditions could have an even more widespread impact on the cardiovascular and metabolic consequences than any of the conditions on their own (Lévy *et al.,* 2009). Atheroma formation leading to atherosclerotic vascular diseases, on the other hand, is considered as a slow process, with its onset believed to begin years before any symptoms appear. OSA also progresses from mild sleep disordered breathing to more severe OSA

over a varying period of time, which may be surprisingly short in the case of weight gain and lack of effective treatment (Berger *et al.,* 2009; Sahlman *et al.*, 2010). In summary, for all these conditions, weight reduction and increased physical activity should be the first-line treatment when they are linked to excess body weight. Furthermore, an early intervention is recommended to halt the progression of OSA and atherosclerotic vascular diseases in order to prevent the development of serious complications (Table 19.2).

19.8 Importance of weight loss

The improvement of OSA is highly associated with weight loss, and treatment results are comparable to those achieved by weight reduction in other obesity related morbidities. Table 19.3 summarizes the large body of evidence favoring lifestyle modification in the prevention and treatment of all obese related conditions. Weight reduction has been shown to result in a marked improvement in insulin resistance, and in some studies in type 2 diabetics also recovery of normal insulin secretion has been found. In the long-term, weight reduction, increased physical activity and adopting a healthy diet have resulted in a sustained reduction of type-2 diabetes in subjects with impaired glucose tolerance (Lindström *et al.,* 2006). It should scarcely come as a surprise that the same 5% or greater decrease from the original body weight which has such a benefit in type-2 diabetes, also achieves an improvement in OSA (Lindström *et al.,* 2006; Tuomilehto *et al.,* 2009). Previous studies have demonstrated that lifestyle intervention can be an effective

Table 19.2. Benefits of features achieved by weight reduction in cardio-metabolic syndrome.

Variable/risk factor[1]	Change	Evidence[2]
Glucose tolerance	improvement	A, prevention of diabetes on long-term in people with IGT[1]
Insulin sensitivity	improvement	A
Blood pressure	decrease	A
Low grade inflammation	decrease	B
Triacylglycerol concentration	decrease	A
Total and LDL cholesterol	small decrease	A
LDL cholesterol	increase	A
Autonomic nervous function	could be improved	B
Left ventricular function	could be improved	B

[1] HDL-cholesterol = high density lipoprotein cholesterol; LDL-cholesterol = low density lipoprotein cholesterol; IGT = impaired glucose tolerance

[2] Evidence grade A – strong scientific evidence: supported by at least two studies with high study quality and relevance among the total scientific evidence; evidence grade B – moderately strong scientific evidence: supported by at least one study with high study quality and relevance as well as two studies with medium study quality and relevance among the total scientific evidence.

Table 19.3. Main randomized controlled studies on the effects of lifestyle intervention on obstructive sleep apnea (OSA), type-2 diabetes or cardiovascular diseases.

Study	Country	Objective	Subjects (n)	Follow-up (months)	Weight loss in kg (% from baseline)	Main results
Tuomilehto *et al.*, 2010	Finland	OSA	82	24	8 (8)	improvement of OSA
Foster *et al.*, 2009	USA	OSA	264	12	11 (11)	improvement of OSA
Saaristo *et al.*, 2010	Finland	type-2 D	2,798	12	1 (1)	reduction in diabetes
Knowler *et al.*, 2009	USA	type-2 D	2,766	120	2 (2)	reduction in diabetes
Lindström *et al.*, 2006	Finland	type-2 D	522	84	2 (2)	reduction in diabetes
Ilanne-Parikka *et al.*, 2008	Finland	MeS	522	48	3.5 (4)	reduction in MeS
Bo *et al.*, 2007	Italy	MeS	335	12	1 (1)	reduction in MeS
Wing, 2010	USA	CVD	5,145	60	8 (9)	reduction in CVD risk
Foster *et al.*, 2010	USA	CVD	307	24	7 (7)	reduction in CVD risk
Burke *et al.*, 2005	Australia	hypertension	241	4	3.3 (4)	reduction in BP
Kastarinen *et al.*, 2002	Finland	hypertension	715	24	1.5 (2)	reduction in BP

OSA = obstructive sleep apnea; Type-2 D = type-2 diabetes; MeS = metabolic syndrome; CVD = cardiovascular disease; BP = blood pressure

prevention tool for high risk individuals, e.g. those with impaired glucose tolerance, and the beneficial effects are sustained over the long-term. Why then should it be any different for OSA? In view of the high prevalence of obesity and the unsatisfactory adherence of some patients to CPAP treatment, weight loss by lifestyle changes in well-designed programs, and in severe cases by bariatric surgery, offer an interesting and viable option alongside the conventional treatment modalities of OSA. However, there is an urgent need for large-scale well-designed and executed studies to further clarify the role of permanent weight loss in the treatment of OSA as well as the development of clinically relevant lifestyle intervention programs for these patients, particularly to evaluate the effects of bariatric surgery before any definite conclusions in terms of clinical significance of weight loss can be included into the current clinical guidelines of OSA treatment. However, even at this point, for overweight OSA patients we strongly recommend long-term weight reduction by changing lifestyles since it has such a beneficial effects on the cardiometabolic sequel of obesity as well as a general improvement in wellbeing (Table 19.4).

19.9 Conclusion

Based on the current knowledge, sustained weight reduction is a very effective treatment modality in overweight patients with OSA, and therefore, weight reduction should always be included in

Table 19.4. Changes in the cardio-respiratory recordings, body weight, body mass index (BMI), and waist circumference after the 12 months' intervention. The data represent mean changes with standard deviation (SD) (Tuomilehto et al., 2009. Reprinted with permission of the American Thoracic Society. Copyright by American Thoracic Society).

	Control group	Intervention group	P-value[1]	P adj[2]
Number of patients with follow-up data	37	35		
AHI-total[3]	0.3 (8.0)	-4.0 (5.6)	0.011	0.017
Number of cured patients, N (%)[4]	13 (35)	22 (63)	0.033	0.019
Apnea indices separately per hour	1.3 (5.1)	-0.9 (2.4)	0.029	0.005
Hypopnea indices separately per hour	-0.9 (4.3)	- 3.5 (4.1)	0.013	0.053
Mean arterial oxygen saturation	-0.3 (1.3)	0.8 (1.2)	<0.001	0.002
Percentage with arterial oxygen saturation below 90%	1.8 (6.3)	-1.7 (4.1)	0.016	0.042
Heart rate (beat/min)	1.1 (5.0)	-2.8 (5.8)	0.081	0.075
Weight, kg	-2.4 (5.6)	-10.7 (6.5)	<0.001	<0.001
Body mass index, kg/m^{2}	-0.8 (2.0)	-3.5 (2.1)	<0.001	<0.001
Waist circumference, cm	-3.0 (6.0)	-11.6 (6.6)	<0.001	<0.001
Plasma glucose, fasting, mmol/l	-0.4 (1.4)	-0.6 (2.3)	0.52	0.30
Plasma insulin, mU/l	-1.2 (3.4)	-5.9 (7.0)	<0.001	0.004
Serum HDL cholesterol, mmol/l	0.05 (0.22)	0.14 (0.22)	0.085	0.103
Serum triglycerides, mmol/l	-0.06 (0.65)	-0.48 (1.13)	0.054	0.027
Systolic blood pressure, mm Hg	-1.1 (19.6)	-1.7 (14.7)	0.88	0.47
Diastolic blood pressure, mm Hg	-0.4 (12.6)	-1.9 (10.6)	0.62	0.87
Snore outcomes survey	11.8 (12.6)	19.0 (14.2)	0.025	0.001
Witnessed apneas, N (%)	33 (97)	23 (74)	0.011	<0.001

[1]P-value = Fisher's exact test or t-test for equal change between groups; [2]P adj = test for equal change between groups, adjusted for age, sex, body mass index, and baseline level of respective variable; [3]AHI = apnea-hypopnoea index (the number of apnea-hypopnoea events with at least a 4% oxygen desaturation per hr); [4]Cured = defined as apnea-hypopnea index <5 events/hr.

the treatment of OSA when this is linked to excess weight. In addition to improving OSA, weight reduction also improves the other obesity related disturbances of cardiometabolic syndromes, e.g. the increased risk for cardiovascular diseases and type-2 diabetes. The cornerstone of treatment of overweight patients must be weight reduction by lifestyle changes (healthy eating habits, food behavior therapy, if needed, and physical activity) and this should be the first-line treatment for all OSA patients. If necessary, bariatric surgery may represent an option in carefully selected patients who are severely obese.

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Summary points

- Diabetes mellitus (DM) and obstructive sleep apnoea (OSA) are very common diseases that affect a continuously increasing proportion of adult population across the world.
- Currently, we witness the evolving epidemic of overweight and obesity and DM, each of those closely associated with substantial risk of OSA.
- Both type 2 diabetes and OSA are associated with serious consequences comprising reduced quality of life, increased risk for disability and suffering from cardiovascular diseases in form of stroke or heart disease and even premature death.
- Type 2 diabetes and OSA can remain undetected over a long period of time while causing metabolic derangement with subsequent organ damage of the unaware affected individual.
- Type 2 diabetes and OSA share common risk factors which can be altered to a high extent by informed and focused life style changes comprising avoidance of tobacco smoking, weight control, modification of dietary habits and regular physical activity.
- The concomitance of both diseases is related to a dismal prognosis while the extent of harm can to large extent be limited by adequate treatment combined with preventive measures that should be introduced without delay.

20. Diabetes mellitus and obstructive sleep apnoea

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Abstract

The global prevalence of diabetes mellitus (DM) has reached 366 million in 2011 with the majority being between 40 and 59 years of age. The increasing prevalence of DM is mainly attributed to the epidemics of obesity and aging. Obstructive sleep apnoea (OSA) is also a common condition. Both are known for their impact on cardiovascular morbidity, reduced quality of life, disability, high health care expenditures and premature death. Both conditions can under a long period of time remain undetected. Both diseases share common risk factors, which can to high extend be modified by informed and focused life style changes comprising avoidance of tobacco smoking, weight control, modification of dietary habits and regular physical activity. Improving the knowledge about the common risk factors predisposing for the development of DM as well as OSA might inspire health care community to screen high-risk individuals and initiate adequate treatment combined with the preventive life style changes. The current article reviews the clinic- and population-based epidemiologic studies as well as pathopysiological mechanisms of the relationship between OSA and DM. Available data regarding the impact of treatment of OSA on DM is also addressed.

Keywords: diabetes mellitus, obstructive sleep apnoea, insulin resistance, obesity, cardiovascular disease, prevention

Abbreviations

AHI	Apnoea-hypopnoea index
BMI	Body mass index
CPAP	Continuous positive airway pressure
DM	Diabetes mellitus
OSA	Obstructive sleep apnoea

20.1 Introduction

Sleep-disordered breathing and its most common form, OSA are associated with insulin resistance and impaired glucose tolerance, which are the main features of type 2 DM. DM and OSA share common risk factors and have many similar features. Both are chronic conditions known for their impact on cardiovascular morbidity, reduced quality of life, disability, high health care expenditures and premature death (WHO/IDF, 2006; Shaw *et al.,* 2008).

The alarming pace of increasing prevalence of DM has reached an unprecedented level that justifies announcement of diabetes epidemics. In the year 2030 almost 10% of the general population aged 20-79 years is expected to have DM (Whiting *et al*., 2011) Similar trends have been seen in the increasing prevalence of sleep-disordered breathing. The epidemics of obesity, diabetes and OSA are closely interrelated. However, the substantial numbers of individuals affected with diabetes or OSA are likely to be unaware neither of their health condition nor the health risks associated with it (WHO/IDF, 2006; Epstein *et al.,* 2009; Lloberes *et al.,* 2011).

20.2 Diabetes mellitus

The term diabetes was for the first time used for description of a disease characterised by passing excessive amounts of urine (polyuria) by a Greek physician, Areateus, living in the second century. Later on, the term has been completed with the Latin word 'mellitus' referring to the sweet taste of the urine from those having diabetes.

In fact, DM is a common name comprising a group of chronic metabolic disorders characterised by hyperglycaemia. Elevated blood sugar reveals dysregulation of glucose metabolism that may be driven by various mechanisms including decreased secretion of the insulin hormone by the pancreas, decreased glucose utilisation or increased glucose production. These various mechanisms may occur either alone or in combination, as in case of type-2 diabetes. In case of destruction of insulin producing β-cells (DM type 1) or genetic defects the disease cannot be prevented. The contrary is true for the predominant type-2 diabetes accounting for 85-90% of all diabetes cases globally. The development of diabetes type 2 is largely preventable and its occurrence can at least be substantially postponed (WHO, 2010; WHO/IDF, 2006).

The metabolic deregulation associated with diabetes affects various metabolic pathways leading to damage of multiple organ systems and adverse outcomes in form of both micro- and macro-vascular complications. DM was recognised as a serious general disorder for the first time by Paracelsus the in the 16th century. This statement remains disturbingly true in the 21st century due to the overwhelming burden of diabetic complications. Diabetes is the predominant cause of death in the most developed countries and in many developing and newly industrialised countries. 48% of deaths related to diabetes occur in people under the age of 60 years. According to the recent data from the World Health Organisation, diabetes is the leading cause of renal failure in the world and the leading cause for visual impairment and blindness in the developed countries (WHO, 2010; WHO/IDF, 2006; IDF, 2011).

There is abundant evidence that microvascular diabetes complications that can present in form of visual impairment or loss, impairment of kidney function or kidney failure requiring dialysis or nerve damage, can to large extend be prevented. Following the accumulating evidence the World Health Organisation has repeatedly revised the criteria for diagnosis of DM (in 1965, 1998 and 2006) to enable disease recognition in its early stages and to promote early introduction of glucose lowering treatment as well as early prevention and treatment of diabetic complications (WHO/IDF, 2006).

20.3 Obstructive sleep apnoea

OSA is characterised by repetitive episodes of partial or complete upper airway obstruction during sleep causing hypopnoea or apnoea and oxyhemoglobin desaturation (hypoxemia) resulting in sleep fragmentation (brain awakenings, arousals).

OSA is the most common type of sleep-disordered breathing, accounting for more than 80% of all cases. Sleep apnoea is commonly associated with habitual loud snoring, witnessed breathing pauses while asleep (apnoea, gasping or choking), non-restful sleep, frequent arousals and/or awakenings, repeated urine passing during night or morning headache. (Epstein *et al.,* 2009; Lloberes *et al.,* 2011)

As far as the diagnostic criteria are concerned, obstructive sleep apnoea is recognised in case of at least five respiratory events in form of apnoea or hypopnoea and arousals associated with oxyhemoglobin desaturation per hour sleep in the presence of typical symptoms (see above). In the absence of sleep related symptoms, the diagnosis is justified if there are least 15 respiratory apnoea-hypopnoea events per hour of sleep (AHI≥15). (Epstein *et al.,* 2009; Lloberes *et al.,* 2011)

The immediate consequences of OSA are sleep fragmentation and sleep debt, which result in fatigue and excessive daytime sleepiness. The consequences of OSA are however much more pronounced involving metabolic derangement involving various intermediate mechanisms comprising energy processing, insulin resistance, endothelial dysfunction, oxidative stress,

hypercoagulability and systemic inflammation affecting multiple organs and systems in the body as presented in Figure 20.1.

In response to obstructed airflow the body strives to restore it by activation of respiratory muscles, leading to abrupt pressure changes within the chest (↓ thoracic pressure). Hypoxemia, obstructed air flow and abrupt changes of thoracic pressure disturb the resting brain (slow waves sleep) and lead to cortical activation and trigger activation of the sympathetic nervous system to prepare various organs to counteract the stress of disrupted airflow as shown in the upper part of Figure 20.2.

These disturbing events result directly in increased heart rate and blood pressure and trigger a chain of intermediate mechanisms comprising insulin resistance, endothelial dysfunction, oxidative stress, hypercoagulability, ventricular dysfunction of the heart and generalised systemic inflammation (middle part of Figure 20.2, by Lloberes *et al.,* 2011).

The repetitive disruption of airflow during the night activates a number of complex mechanisms aiming to restitute the air flow and compensate for the metabolic disturbances caused by apnoea/hypopnoea episodes. The presence of OSA leads to rearrangement of the energy balance in the body affecting use of energy, its availability, utilisation and storage promoting especially visceral fat accumulation, as presented in Figure 20.2.
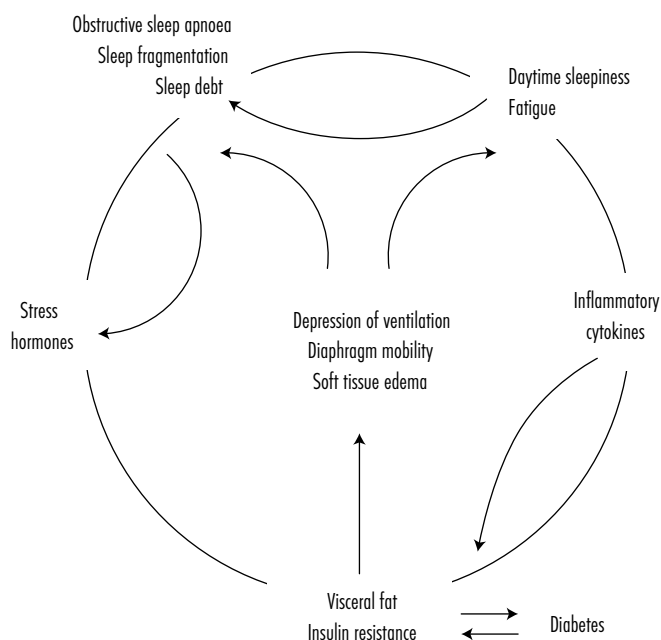
Figure 20.1. Photogenic mechanisms of cardiovascular consequences of obstructive sleep apnoea (OSA) (modified from Lloberes *et al.*, 2011: Figure 1, p. 147).
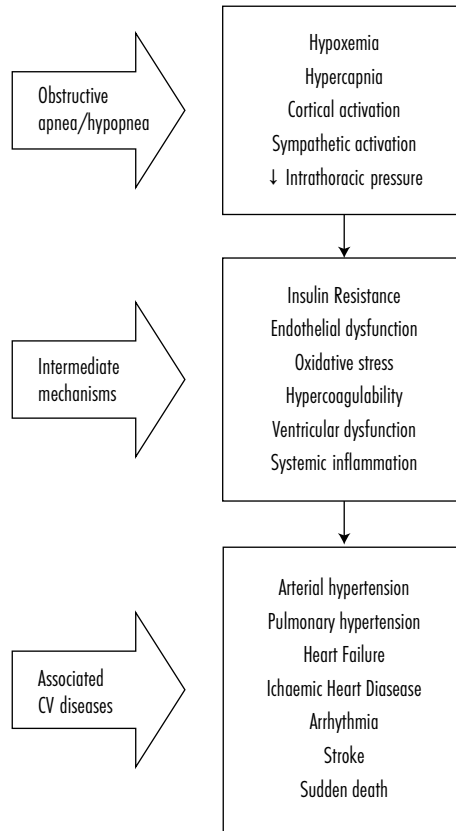
Figure 20.2. A heuristic model of complex feed forward associations between visceral fat/insulin resistance, inflammatory cytokines, stress hormones, excessive daytime sleepiness and sleep apnoea (modified from Vgontzas *et al.,* 2003: Figure 6, p. 37).
CV = cardiovascular

20.4 Epidemiology

20.4.1 Prevalence of diabetes mellitus and obstructive sleep apnoea in general population

The global prevalence of DM accounts currently for 4.4% among the adult population (20-79 years) with seven million of patients with diabetes around the world. Despite the differences in economical conditions and life habits, the number of people with type-2 diabetes is increasing in every country. There are substantial differences in the national prevalence figures between various regions and countries ranging from the lowest prevalence (1.5-4%) in Mali, Moldova, Iceland, moderate (<10%) in many European countries, around 10-12% in the most developed and highly populated countries such as Japan, USA and Russian Federation, 20% in Saudi Arabia, Qatar, and the highest (>25%) in Pacific Islands (IDF, 2011). According to the latest estimates there are 366 million people living with DM year 2011 of whom 50% being unaware of the

disease. The majority of people with diabetes are between 40 and 59 years of age. According to the recent assessments, the prevalence of diabetes is expected to reach 552 million by the year 2030, indicating that one in ten adults aged 20-79 years will have DM.

The main causal factor for developing type-2 diabetes is the imbalance between energy intake and expenditure stiffed towards energy accumulation commonly in form of visceral fat, associated not only with abdominal obesity but also with reduced physical activity and often due to other unhealthy behaviours. Overweight and obesity are very common among patients with type-2 diabetes accounting for 42% and 37%, respectively, as shown in a large study of the French population (Hilliert *et al.,* 2006). The strongest predictors of type-2 diabetes for an individual are impaired glucose tolerance and metabolic syndrome, both related with insulin resistance.

20.4.2 Prevalence of obstructive sleep apnoea

Based on the population-based studies from different continents and countries OSA is to be found in 9 to 26% of middle-aged population (Lloberes *et al.*, 2011; Young *et al.*, 1993).

Recent longitudinal studies reveal that OSA is a progressive disease with a clear tendency of AHI to progress over time even in individuals who sustain their baseline weight (Epstein *et al.,* 2009; Newman *et al.,* 2005). The prevalence of OSA is increasing with aging with more than 25% of population from 65 years of age and above.

In general, OSA is more common in men than women but this sex-disparity disappears entirely after menopause. The knowledge regarding OSA in women is fairly limited. It should be emphasised that women seem to have different patterns and symptoms as well as natural history of the disease, than men (Lloberes *et al.,* 2011; Newman *et al.,* 2005). The prevalence of OSA associated with the cardinal symptom of daytime sleepiness is approximately 3 to 7% for adult men and 2 to 5% of adult women. Importantly, the vast majority (70-80%) of affected individuals is unaware either of the associated symptoms or of the disease.

In similar to the risk of type-2 diabetes, the risk for OSA is closely related with excessive bodyweight, especially abdominal obesity, as the number of apnoea/hypopnoea episodes per hour (AHI) increases along with increasing measures of BMI or waist circumference (Lloberes *et al.,* 2011).

20.4.3 Prevalence of diabetes mellitus in obstructive sleep apnoea population

The concomitance of OSA and DM has become increasingly recognised within the last 20 years. One of the first reports came from Katsumata *et al.* in 1991 who investigated the prevalence of OSA among a large population of over 12 thousands patients (6,554 men and 6,233 women) visiting the hospital in the city of Nagoya in Japan. OSA was more common among patients with known diabetes or hypertension compared to that among non-diabetic and normotensive individuals. On the other hand, screening of the newly diagnosed OSA subjects with an oral

glucose tolerance test revealed that 77% had an altered glucose metabolism, and one third of the OSA subjects demonstrated DM, which was unrecognised before the study. These results have been confirmed by several population-based studies with main results presented in Table 20.1.

One of the largest studies addressing the issue of strong interrelations between type-2 diabetes and OSA in a systematic manner was the Sleep Heart Health Study with over two and a half thousand participants (Punjabi *et al.,* 2004). The prevalence of impaired glucose tolerance (36%) or diabetes (15%) were substantially higher in participants with OSA compared to that among subjects without OSA (29% and 9%, respectively). Diabetes diagnosis was five times more common among participants with moderate to severe OSA (AHI≥15) compared to those without OSA (14.7% versus 2.8%) in the cross-sectional analysis of the Wisconsin Sleep Cohort. Patients with moderate to severe OSA have more than doubled risk for having concomitant diabetes (odds ratio of 2.3), with a strong linkage remaining statistically significant even after adjustment for age, sex and body habitus (Reichmuth *et al.,* 2005).

In summary, multiple population-based studies confirm complex and strong associations between obstructive sleep apnoea and altered glucose metabolism, insulin resistance and type-2 diabetes independently of age, gender and body habitus. Furthermore, the severity of OSA estimated by the number of apnoea-hypopnoea episodes and degree and duration of hypoxemia predicts worsening of glucose tolerance and enhances insulin resistance.

20.4.4 Prevalence of obstructive sleep anoea in patients with diabetes mellitus

Several population-based studies found OSA to be at least twice more common in men with type-2 diabetes compared to their normoglycaemic counterparts, even after adjustment for body habitus or central obesity (Elmasry *et al.,* 2001; Tasali *et al.,* 2008a; West *et al.,* 2006). Concomitance of OSA and DM has been a subject of numerous publications in the recent years with the reported prevalence of moderate or severe OSA (AHI≥15) ranging from 17 to 60% among patients attending diabetes clinics. The figures reported for women being about one half of those for men (Babu *et al.,* 2005; Einhorn *et al.,* 2007; Shaw *et al.,* 2008; West *et al*., 2006). There seems to be no doubt that patients with type-2 diabetes have especially high risk for OSA, at least due to the high prevalence of obesity. It is to be recognised that the figures are influenced by factors related to the characteristics of the specific patient sample, the presence of accompanying diseases as well as the severity of the sleep-disordered breathing.

20.4.5 Incidence of diabetes mellitus in longitudinal studies

Considering the pathogenetic mechanisms linking OSA with insulin resistance and altered glucose tolerance as presented in Figure 20.1, it would be plausible to expect an high incidence of diabetes among patients with known OSA. Indeed, several population-based studies investigated this important question. Hitherto accumulated data indicate an increased incidence of type-2 diabetes in subjects with OSA compared to their non-OSA counterparts, however larger samples and longer observation time might be needed to confirm this hypothesis beyond the

Table 20.1. Population-based studies linking obstructive sleep apnoea (defined by polysomnography) and altered glucose metabolism or type-2 diabetes (modified from Tasali et al., 2008a: Table 1, p. 497).

Study	Sample all (women)	Characteristics country	Measures of GM[1]	Main findings[2]
Katsumata et al., 1991		hospital visitors Japan	OGTT	1. high prevalence of OSA in men, subjects with HT or DM 2
Stoohs et al., 1996*	50 (34)	healthy overweight USA	IR, insulin suppression test	↑IR in OSA depends on BMI
Elmasry et al., 2001	116	Hypertensive Sweden	FPG, HOMA	1. Moderate OSA (AHI≥20) was twice as common in patients with DM compared to subjects with normoglycaemia[1] 2. OSA severity is related to indices of IR in non-DM subjects[1]
Punjabi et al., 2002	155	middle aged (≥45y), mildly obese/USA	OGTT, HOMA	↑AHI was associated with ↑IR independent of obesity.
Ip et al., 2002	270 (73)	China	HOMA	OSA (AHI and minimum oxygen saturation) is independently associated with IR[1]
Punjabi et al., 2004	2,656 (1,442)	Sleep Heart Health Study USA	OGTT, HOMA	1.OSA (AHI & oxygen saturation) is associated with glucose intolerance and IR[1] 2. OSA severity related to degree of IR[1].
Reichmuth et al., 2005	1,387 (608)	Wisconsin Sleep Cohort USA	DM diagnosis or FPG≥126 mg/dl	DM is 2.3 times more prevalent in subjects with OSA (AHI≥15)[1]
Lam et al., 2006[3]	255 (155)	China	FPG	OSA (AHI≥5) is related to ↑FPG[1]
Okada et al., 2006[3]	207	Japan	HbA1c, FPG	OSA (AHI≥15) is associated with higher FPG & HbA1c than non-OSA patients with similar BMI.
Sulit et al., 2006	394 (217)	Cleveland Family Study USA	OGTT	Hypoxic stress (≥2% time with oxygen saturation <90%) doubles the odds of IGT[1].

[1] OSA = obstructive sleep apnoea defined by polysomnography; DM = diabetes mellitus; OGTT = oral glucose tolerance test; FPG = fasting plasma glucose; HbA1c = glycated haemooglobin A1c; HOMA = homeostasis model assessment used as a surrogate measure of insulin resistance; IR = insulin resistance (often assessed by means of HOMA); HT = hypertension; GM = glucose metabolism.

[2] Independent from age, gender, body habitus or BMI (in some studies even smoking, alcohol use).

[3] details for references to be found in Tasali et al., 2008.

doubts (Marshall *et al.*, 2009; Reichmuth *et al.*, 2005). The most recently published data, based on 16-years long observation of patients with confirmed diagnosis of OSA suggest that incidence of diabetes may differ between sexes. Celen *et al.* (2010) found that OSA was strongly related to the incidence of type-2 diabetes in women while the incident cases of DM diagnosis could be mainly dependent on the changes in BMI or weight in men.

20.5 Pathophysiology

There is a wealth of evidence from epidemiological and clinic-based studies indicating a close interrelation between sleep-disordered breathing and altered glucose regulation, as reviewed by Tasali and colleagues (2008a). The causative mechanisms for insulin resistance in OSA have been eagerly studied. Two research groups have confirmed that insulin resistance could not be sufficiently explained by obesity (Ip *et al.,* 2002; Punjabi *et al.,* 2002). An independent correlation was identified between insulin resistance and the number of apnoea-hypopnoea events (AHI) and minimal desaturations during sleep. These findings were further verified by means of repeated blood glucose measurements and a standardised oral glucose tolerance test among non-diabetic participants of a large cross-sectional Sleep Heart Health Study. Punjabi and colleagues (2004) demonstrated that the number of AHI episodes associated with at least 4% decrease in oxygen saturation, are related to glucose tolerance and insulin resistance from mild to severe OSA independently of age, sex, BMI and waist circumference. The causative impact of sleep curtailment on feature insulin resistance, including insulin sensitivity, glucose effectiveness and pancreatic insulin secretion, assessed by an intravenous glucose tolerance test, was examined in experimental studies performed on healthy volunteers. (Spiegel *et al.,* 1999; Tasali *et al.,* 2008b). Spiegel and associates investigated metabolic features assessed by an intravenous glucose tolerance test conducted after six nights of sleep restricted to 4 hrs compared with fully rested condition following seven nights with 12 hr sleep in eleven healthy men. The experimental sleep-debt caused a significant worsening of glucose clearance with a 40% and 30% reduction of acute insulin response to glucose injection and higher blood glucose levels following breakfast. Thereby experimental restriction of sleep time has been proven to impair glucose regulation in the healthy volunteers to a degree known for older adults with impaired glucose tolerance, known as a precursor of DM type 2.

Interestingly, similar alterations of glucose regulations were induced by suppression of a slow-wave sleep by acoustic stimuli with sustained total sleep time (Tasali *et al.,* 2008b). The degree of slow-wave sleep reduction was strongly correlated with decrease of insulin sensitivity which in turn was directly associated with increased sympathetic activity during the day. Thereby not only sleep duration but also sleep quality seems to affect the regulation of glucose metabolism.

Different aspects of sleep quality may be relevant for people with untreated OSA, who encounter restricted volume of air flow in form of apnoea-hypopnoea events as well as hypoxemic stress defined by the minimal oxyhemoglobin desaturation and the time of hypoxemia. Sulit and colleagues (2006, Table 1) investigated the polysomnographic features and glucose tolerance

(by an oral glucose tolerance test) in 394 participants of Cleveland Family Study. The strongest association was found between the duration of oxygen desaturation below 90% and the prevalence of impaired glucose tolerance. Subjects who had hypoxemia (<90%) for longer than 2% of sleep time were 2.3 times more likely to have impaired glucose tolerance. On the other hand, the frequency of arousals was associated with mild increase in risk of hypertension.

In summary, restriction of sleep time as well as impairment of sleep quality enhances activation of sympathetic activity that is directly related to increased glucose concentrations, impairment of glucose tolerance and decreased insulin secretion and sensitivity even in healthy humans. There might be several different mechanisms affecting glucose regulation among patients suffering from OSA (Figure 20.1). According to the currently available knowledge, exposure to hypoxemic stress might have the strongest causative impact on dysregulation of glucose tolerance and possibly modulation of insulin resistance.

The endocrine and metabolic consequences of sleep curtailment effect not only glucose regulation but also energy turnover with a positive feed forward pressure for visceral fat accumulation (Vgontzas *et al.,* 2003: Figure 1).

20.6 Cardiovascular consequences of diabetes mellitus and obstructive sleep apnoea

The mechanisms of cardiovascular outcomes in diabetes are in general related to hyperglycaemia (starting from the entirely normal glucose levels), distorted intracellular energy turnover and systemic inflammation combined with hypercoagulability and endothelial dysfunction (WHO/IDF, 2006; WHO, 2010). A number of similar intermediate mechanisms are involved in the mechanisms of the cardiovascular complications caused by OSA, as presented in Figure 20.2.

Globally, diabetes is the leading cause of cardiovascular deaths among the adults. People with diabetes have more than doubled risk for cardiovascular diseases such as heart attack (myocardial infarction) or stroke and premature death compared to their peers without DM. In the global perspective as many as 4.6 million of premature deaths are annually attributable to diabetes (IDF, 2011).

According to the recent large observational studies, OSA, defined as 15 or more apnoea/hypopnoea events per hour of sleep (AHI≥15), is independently associated with increased risk for cardiovascular morbidity and mortality, regardless of the presence of symptoms. The increased risk for cardiovascular complications is especially pronounced in men with untreated severe apnoea (AHI≥30), with hazard ratio of 5.2 for cardiovascular and 3.8 for all-cause mortality (Marin *et al.,* 2005; Yaggi *et al.,* 2005; Young *et al.,* 2008).

20.7 Impact of obstructive sleep apnoea treatment on diabetes control

Considering the causative impact of OSA on the glucose metabolism, introduction of the treatment of OSA with CPAP could be expected to improve glucose regulation. The impact of CPAP treatment on glucometabolic regulation has been eagerly tested among DM patients in the recent years with a variable success. As far as the impact of CPAP-power on the measures of insulin resistance is concerned, the majority of studies could show positive improvements regarding the real-time glucose measurements and symptomatic improvements (Babu *et al.,* 2005; Dawson *et al.,* 2008). However, only one randomised clinical trial addressing this issue has been published to date. West *et al.* (2007) failed to achieve any improvement of the long-term glucose levels estimated by glycosylated haemoglobin A1c by CPAP-treatment alone (WHO/IDF, 2006). Unfortunately, that study was based on a relatively small sample of 20 patients in each arm, and satisfactory use of CPAP has not be ascertained (<4 hrs daily), which might additionally have weakened the study. It should also be kept in mind that striving for improvements in glycosylated haemoglobin A1c levels is a very complicated challenge as glycaemic regulation is influenced by multiple factors comprising not only physiological mechanisms but also human dietary habits and behaviour. It is possible that larger patient populations and effective CPAP-treatment, preferably of longer duration, are needed if the potential treatment effect is to become apparent.

20.8 Impact of weight reduction on obstructive sleep apnoea and diabetes mellitus

Another or complementary treatment option has recently been shown to be effective in patients with DM type 2 and moderate to severe OSA (Foster *et al.*, 2009). Participants of the Sleep AEAD Study having type 2 DM, substantial obesity (mean BMI 36.7 kg/m2) and OSA (mild, 39%; moderate, 35%; severe, 26%; respectively) were randomly assigned to a behavioural weight loss programme based on an Intensive Lifestyle Intervention or a more conventional alternative of three meetings with Diabetes Support and Education sessions. Interestingly, after one year of this study, only 5% of participant were using their CPAP. Patients participating in the intensive lifestyle intervention managed to loose over 10 kg of weight. Compared with their counterparts who followed the more conventional treatment approach, patients from the intensive group improved in their AHI and one third of them achieved total remission of their OSA, while twice many than in comparative group improved in their OSA category. In addition to study results, the authors draw attention to a significant progression of AHI among patients from the conventionally treated group with an increase by four apnoea/hypopnoea events per hour despite unchanged weight. Thus, these results underline the potential of lifestyle modification and preventive actions suggesting that effective weight reduction can be successful even in the most demanding patient populations.

20.9 Guidelines and recommendations

Universal recommendations appropriate for anyone comprise a combination of:
- weight management;
- healthy eating habits;
- regular exercise;
- regular and adequate sleep.

All of which improve insulin sensitivity, facilitate weight control, improve physical fitness and overall wellbeing.

According to the most recent guidelines food products with starches and carbohydrates that are more slowly digested and absorbed (low glycaemic index food) are beneficial in improving glycaemic control in people with diabetes or impaired glucose tolerance (IDF, 2011).

The specific guidelines regarding DM and OSA as well as the general recommendations from the WHO and IDF include active screening of individuals known to have high risk for cardiovascular complications that can be prevented by adequate treatment and intensive lifestyle changes:
- Examine all patients with DM for potential OSA:
  a. in case of confirmed co-diagnosis introduce available treatment (CPAP or alternative);
  b. OSA treatment can improve blood pressure and glycemic control, facilitate weight reduction, and not in the least, improve patient's quality of life.
- Examine all patients with OSA for impaired glucose tolerance/hyperglycaemia:
  a. if confirmed, refer for specific treatment and preventive life style intervention;
  b. lifestyle intervention for preventing type-2 diabetes in people at high risk can reduce incidence of DMt2 by 35-58%
- Recommend & support & facilitate introduction of life style changes in subjects with recognised OSA or DM alone or in combination.
- Recommend & support & facilitate adequate risk factors management in those with DM or OSA or both.

Acknowledgement

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Summary points

- Malnutrition is common in patients with Crohn's disease (CD).
- Enteral nutrition (EN) is frequently required in patients with CD.
- The most serious limitation of EN with an elemental diet (ED) is inadequate patient compliance.
- The application of a nasogastric tube is useful and recommended during ED therapy.
- EN therapy with nocturnal enteral support is effective in inducing and maintaining clinical remission in patients with CD.
- EN therapy with nocturnal infusion of ED shows a clear suppressive effect on endoscopic disease activity and mucosal cytokine production.
- Nocturnal tube feeding is helpful for patients to take enough calories to maintain a good nutritional status.
- Further studies are necessary to better understand the mechanisms of action of nocturnal EN in patients with CD.

21. Enteral support at sleep time in Crohn's disease

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Abstract

Malnutrition is frequently observed in patients with Crohn's disease (CD). Enteral nutrition (EN) has often been used as an adjunct therapy to correct or to avoid malnutrition. In Japan, EN is the first line therapy for both active and quiescent CD. Patients with acute exacerbations are treated by exclusive elemental diet (ED) therapy: continuous ED infusion through a nasogastric tube in both the daytime and nighttime. After achieving clinical remission, patients are treated with half ED therapy: approximately half of the calories are taken from ED. A nasogastric tube is self-intubated every night, and the ED is infused continuously through the tube using an infusion pump in the nighttime. In the daytime, low fat foods are taken in accord with instructions of dieticians. Recently, the author and colleagues conducted clinical trials investigating the efficacy of EN therapy with nocturnal infusion of ED. The outcomes of our trials show that EN therapy is effective in inducing and maintaining clinical remission. During enteral support at sleep time, no serious problems are observed, and this procedure does not disturb sleep. Nocturnal ED infusion through a nasogastric tube is helpful for patients to take enough calories to maintain a good nutritional status.

Keywords: Crohn's disease, elemental diet, enteral nutrition, nocturnal enteral support, nutritional status

Abbreviations

BMI	Body mass index
CD	Crohn's disease
CDAI	Crohn's disease activity index
CI	Confidence interval
ED	Elemental diet
EN	Enteral nutrition
FA	Fatty acid
i.q.r.	interquartile range
IL	Interleukin
IL-1ra	Interleukin-1 receptor antagonist
OR	Odds ratio
PD	Polymeric diet
PSL	Prednisolone
PUFA	Polyunsaturated fatty acid
TNF	Tumour necrosis factor

21.1 Introduction

Crohn's disease is a chronic inflammatory bowel disease characterized by a relapsing-remitting course with trans-mural inflammation of potentially any section of the digestive tract, leading to various clinical manifestations (Farmer *et al.*, 1975). The disease represents an important public health problem, as it tends to affect young people and have a chronic course affecting quality of life, working abilities and social activities. The most common symptoms of CD include diarrhoea, abdominal pain, weight loss and fever (Baumgart and Sandborn, 2007). Extra-intestinal manifestations occur in at least 25% of patients with CD. Some extra-intestinal manifestations, such as erythema nodosum and peripheral arthropathy, will wax and wane in keeping with bowel inflammation (Ephgrave, 2007).

Malnutrition is frequently observed in patients with CD, and currently various dietary interventions or supplements are available for such patients (Driscoll Jr and Rosenberg, 1978; Hodges *et al.,* 1984; Mekhjian *et al.,* 1979). EN has often been used as an adjunct therapy to correct or to avoid malnutrition. In addition, several authors have considered EN as a strategy to induce and maintain remission in patients with CD (Goh and O'Morain, 2003; Hartman *et al.,* 2009; King *et al.,* 1997). In Japan, EN is the first line therapy for both active and quiescent CD (Hiwatashi, 1997; Matsui *et al.,* 2005; Yamamoto *et al.,* 2009). Patients with acute exacerbations are treated by exclusive ED therapy: continuous ED infusion through a nasogastric tube in both the daytime and nighttime. After achieving clinical remission, patients are treated with half ED therapy: approximately half of the calories are taken from ED. A nasogastric tube is self-intubated every night, and the ED is infused continuously through the tube using an infusion pump in the nighttime. Recently, the author and colleagues have conducted clinical trials investigating the

efficacy of EN therapy with nocturnal infusion of ED. In this article, the author will show the detailed outcomes of the clinical trials, and discuss the usefulness of nocturnal enteral feeding.

21.2 Diet and the expression of Crohn's disease

The exact cause of CD remains unknown. The rise in the incidence and the prevalence of CD has paralleled the socioeconomic development of populations and adaptation to a Western lifestyle (Loftus Jr, 2004). Diet is thought to be an important factor in the pathogenesis of CD, but whether antibodies against dietary antigens play a primary role in CD aetiology or are secondary to gut inflammation is yet to be established. The number of patients with CD in Japan has increased rapidly during the past three decades (Yamamoto *et al.*, 2009). The increase may be due to introduction of Western lifestyle because the genetic background of the population in Japan is fairly homogeneous and has not changed significantly. The change in diet can be a major factor in the pathogenesis of CD.

A Japanese epidemiologic study (Shoda *et al.*, 1996) found that the increased incidence of CD was significantly correlated with the increased dietary intake of total fat, animal fat, n-6 PUFAs, animal protein, milk protein and the ratio of n-6 to n-3 FA intake. These data suggest that an increased dietary intake of animal protein and n-6 PUFAs with less n-3 PUFAs may contribute to the expression of CD. A Western study (Amre *et al.*, 2007) also reported similar results. Consumption of long-chain n-3 FAs was negatively associated with the development of CD (OR 0.44, 95% CI 0.19-1.00). A higher ratio of long-chain n-3/n-6 FAs was significantly associated with lower risks for developing CD (OR 0.32, 95% CI 0.14-0.71). Their findings indicate that imbalance in consumption of FAs is associated with increased risks for CD.

21.3 Malnutrition in Crohn's disease

Malnutrition is common in patients with CD, with an incidence ranging from 25-80% (Driscoll Jr and Rosenberg, 1978; Hodges *et al.*, 1984; Mekhjian *et al.*, 1979). Malnutrition can be determined by insufficient dietary intake, poor appetite, muscle wasting, and weight loss. In patients with CD, several factors may contribute to malnutrition, including anorexia, malabsorption, drug-nutrient interactions, and increased fluid, electrolyte and blood loss from the gut (Hodges *et al.*, 1984; Mekhjian *et al.*, 1979). Anorexia is often the most prominent cause of malnutrition, which can result from increased levels of several cytokines including TNF-α (Beutler *et al.,* 1985). Patients also may have inadequate intake of nutrients secondary to fear of abdominal cramps and diarrhoea after eating. Malabsorption can be another cause for malnutrition. In patients with small bowel involvement, the surface area available for absorption of nutrients may be decreased by the degree of inflammation present. Decreased absorptive surface area can also result from small bowel resection. Ileal resections can result in vitamin B_{12} deficiencies, and fat and fat-soluble vitamin deficiencies due to bile salt malabsorption (Duerksen *et al.,* 2006). The intestinal inflammation observed in patients with CD is often associated with exudative protein losses, and

the degree of protein loss correlates with disease severity (Hodges *et al.,* 1984). Inflammation also produces a catabolic response, which is probably a cytokine-mediated phenomenon, resulting in a negative nitrogen balance. Patients with active CD should require higher protein intake than the general population without a known gastrointestinal disorder.

21.4 The mechanism of action of enteral nutrition

EN is frequently required in patients with CD. During EN therapy, improvements are observed not only in nutritional status, but also in disease symptoms, and several patients experience complete clinical remissions (Goh and O'Morain, 2003; Hartman *et al.,* 2009; King *et al.,* 1997). However, the detailed mechanisms of action of EN in patients with CD remain unknown. These mechanisms may include improvement in mucosal permeability leading to decreased antigen uptake and less stimulation of the gut-associated immune system (Sanderson *et al.*, 1987), improved cell-mediated immunity (Morain *et al.*, 1981) and altered bowel flora (Crowther *et al.*, 1973). Further investigations would be necessary to better understand the precise mechanisms of action of EN.

21.5. Type of enteral formula

Various enteral formulas are available for EN with the major differences being related to the protein source (Goh and O'Morain, 2003; King *et al.*, 1997). Enteral formulas are classified by the nitrogen source derived from the amino acid or protein component of the formula. ED is created by mixing of single amino acids, and is entirely antigen free. Oligopeptide or semi-ED is made by protein hydrolysis and have a mean peptide chain length of four or five amino acids which is too short for antigen recognition or presentation. PD contains whole protein from sources such as milk, meat, egg or soy. Enteral formulas can be classified more simply as ED (amino acid-based), semi-ED (oligopeptide) and PD (whole protein). ED has minimal fat content, often <2% of total calories. The restriction of fat associated with the use of ED might alter the ratio of eicosanoids (leukotriene B_4, thromboxane A_2, prostaglandin E_2) with subsequent down-regulation of the inflammatory cascade (Fernández-Bañares *et al.*, 1994). In contrast, PD contains more fat (nearly 30% of total calories) and generally more linoleic acid, which is the parent compound of n-6 PUFAs and is a precursor for the synthesis of eicosanoids of the highest pro-inflammatory activity. Recently it has been postulated that differing fat contents and various amounts of substrates for the arachidonic acid cascade may be more important than the nitrogen source (Fernández-Bañares *et al.,* 1994). The enteral formulas that led to the better outcomes tend to have the lower fat content; however, there is no consensus as to which of the three enteral formulas has the highest therapeutic efficacy.

21.6 The role of enteral nutrition in Japan versus Western countries

The precise role of EN in patients with CD remains to be explained. In 2006, the European Society for Clinical Nutrition and Metabolism published guidelines on the role of EN in patients with CD (Lochs *et al.,* 2006). EN is generally indicated for patients with undernutrition and growth retardation. In children, EN is the first line therapy. In adults, EN should be used as sole therapy mainly when treatment with corticosteroids is not feasible. This statement is based on the results of a recent meta-analysis; EN was significantly inferior to steroids in inducing remission (Zachos *et al.*, 2007). In Japan, EN is the first line therapy for both active and quiescent CD in accord with the guidelines of the Ministry of Health, Labour and Welfare (Yamamoto *et al.*, 2009). This guideline is based on the results of uncontrolled studies conducted in Japan. In Japan, EN therapy for patients with CD has been covered by the national health insurance scheme. The author is not sure if a similar scheme for EN is practiced in Western countries.

21.7. Limitation of enteral nutrition

The most serious limitation of EN is inadequate patient compliance. (Hiwatashi, 1997; Matsui *et al.*, 2005; Yamamoto *et al.*, 2009). Poor palatability of an enteral formula, especially an ED occasionally limits the patient's ability to meet energy requirements. It is a challenge for the EN producing industry to provide products that are appetizing and appealing to patients. Although a large number of palatable flavours are now available, patient compliance is still a serious limitation (Yamamoto *et al.*, 2009). The application of a nasogastric tube is useful and recommended. In Japan, many patients receive ED by a self-inserted nasogastric tube and can continue treatment over a long period if necessary (Hiwatashi, 1997; Matsui *et al.*, 2005; Yamamoto *et al.*, 2009).

21.8. Elemental diet therapy in Japan

In Japan, EN therapy is by a slide method, in which patients may increase the amount of ED when the disease activity worsens, or decrease when the disease activity improves (Figure 21.1). Patients with acute exacerbations are treated by exclusive ED therapy if they do not have bowel obstruction or active enteric fistulas. With improvement of clinical symptoms, patients are allowed to take low fat foods in addition to ED, and the proportion of calories derived from foods is gradually increased. After achieving clinical remission, patients receive half ED therapy at their homes. In the case of a recurring exacerbation, the proportion of calories derived from ED is increased again (Hiwatashi, 1997; Matsui *et al.,* 2005; Yamamoto *et al.,* 2009).
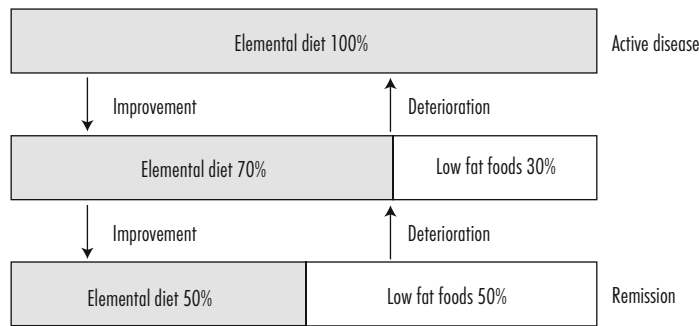
Figure 21.1. Elemental diet therapy in patients with active and quiescent Crohn's disease in Japan.

21.9 Enteral nutrition in our clinical practice

21.9.1 Induction therapy for acute exacerbation

As described before, patients with acute exacerbations are treated by exclusive ED therapy when they do not have bowel obstruction or active enteric fistulas. In our institution, the enteral formula is a commercially available brand, Elental™ (Ajinomoto, Tokyo, Japan), which contains amino acids, vitamins, trace elements, very low fat, and its major energy source is dextrin. A summary of the composition of Elental is shown in Table 21.1. One Elental pack contains 80 g of powdered ED, which is to be dissolved in warm water to give 300 ml of solution before administration. The calorie density is 1 kcal/ml with an osmolarity of 760 mOsm/l. A thin (external diameter, 1.7 mm), soft silicone-elastomer nasogastric tube is intubated, and the ED is infused continuously, in both the daytime and nighttime through the tube using an infusion pump. The concentration of the ED is gradually increased from one-third to the full strength over 7 days (adaptation phase) to reduce side effects such as diarrhoea and abdominal colic. The infusion speed is also increased stepwise from 20 ml/h to the full dose (100-150 ml/h) over seven days (adaptation phase). To avoid low-calorie and low-protein intake and dehydration, intravenous solution including amino acid, carbohydrate and electrolyte is infused during the adaptation phase. After the adaptation phase, a maintenance dose at the full strength is administered. The volume of ED is calculated according to the ideal body weight; approximately 35-40 kcal/kg ideal body weight/day. During acute exacerbations, patients are only allowed tea or water, but no other food during the treatment. To avoid the development of deficiency of essential FAs, intravenous infusion of lipid emulsion (Intralipid™ 20% 100 ml; Terumo, Tokyo, Japan) is given weekly.

In our prospective study, 28 patients (16 males and 12 females; median age, 28 years) with mild-to-moderate active CD were treated with the above-mentioned exclusive ED therapy for four weeks (Yamamoto *et al.,* 2005). The median duration between the diagnosis of CD and entry was 24, i.q.r. 10-42) months. The median CDAI score (Best *et al.,* 1976) was 315 (i.q.r. 265-358) at entry. The ED was infused continuously, in both the daytime and nighttime, through a

Table 21.1. Constituents of Elental at full strength.

	Per 100 ml
Energy	100 kcal
Protein (Amino acids)	4.7 g
Carbohydrate (Dextrin)	21.2 g
Lipid (Soybean oil)	0.16 g
Vitamin A	216 IU
Vitamin D	17 IU
Vitamin B_1	0.06 mg
Vitamin B_2	0.09 mg
Vitamin B_6	0.07 mg
Niacin	0.73 mg
Pantotenic acid	0.37 mg
Folic acid	0.02 mg
Vitamin B_{12}	0.23 µg
Vitamin C	2.6 mg
Vitamin K_1	2.93 µg
Vitamin E	1.1 IU
Biotin	13 µg
Choline	2.87 mg
Na	86.7 mg
K	72.5 mg
Cl	172.3 mg
Mg	13.3 mg
Ca	52.5 mg
P	40.5 mg
Fe	0.6 mg
I	5.1 µg
Mn	100 µg
Cu	66.7 µg
Zn	0.6 mg

nasogastric tube using an infusion pump. The median volume of the ED infused per day was 2,400 (i.q.r. 2,100-2,400) ml.

During the treatment, the majority of patients experienced diarrhoea, abdominal distension or abdominal colic. These symptoms often occurred in the adaptation phase or the early stage of the treatment, and were treated with temporary decreases in the infusion speed and the concentration of the ED. The diarrhoea sometimes required anti-diarrhoeal drugs (loperamide

or codeine). However, these abdominal symptoms were not serious, and could be controlled without an interruption of the treatment. Other adverse effects were not observed during the study, and all patients could complete a four-week treatment without any serious problems. After the four-week treatment, clinical remission was achieved in 20 patients (71%). The median CDAI score was 315 (i.q.r., 265-358) at entry and 127 (i.q.r., 110-285) after treatment. In the majority of patients who achieved remission, significant improvements of clinical symptoms were recognised within two weeks after the start of the treatment. The endoscopic and histological efficacies in both the terminal ileum and the large bowel are presented in Figure 21.2. The endoscopic healing was observed in all of the patients who achieved histological healing. Similarly, clinical remission was observed in all of the patients who achieved endoscopic healing. During the treatment, the mucosal concentrations of interleukin (IL)-1β, IL-1 receptor antagonist (IL-1ra), IL-6, IL-8 and TNF-α in both the ileum and large bowel significantly decreased. Furthermore, the IL-1ra/IL-1β ratio in both the ileum and large bowel significantly increased during the treatment. The endoscopic and histological healing of the mucosal inflammation was associated with a decline of the mucosal cytokines and an increase of the IL-1ra/IL-1β ratio. Body weight, BMI and serum albumin level significantly increased during the treatment (Table 21.2). The following inflammatory parameters significantly decreased during the treatment: white blood cell, platelet, erythrocyte sedimentation rate and C-reactive protein (Table 21.2). The outcomes of this study suggest that four-week exclusive ED therapy achieves clinical remission along with endoscopic healing in the majority of patients with mild-to-moderate active CD. Furthermore, this ED therapy reduces the mucosal cytokine production and corrects an imbalance between pro-inflammatory and anti-inflammatory cytokines.
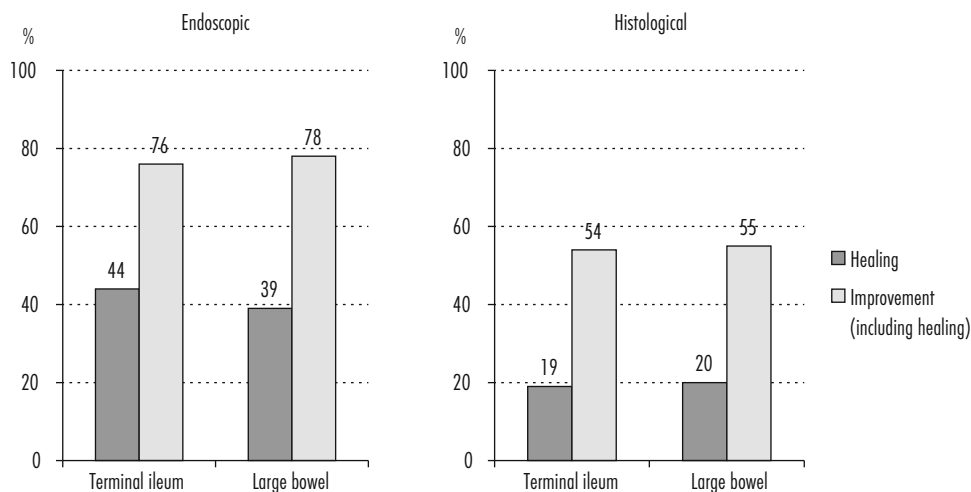
Figure 21.2. The endoscopic and histological efficacies of enteral nutrition for patients with active Crohn's disease.

Table 21.2 Nutritional status and inflammatory parameters before and after treatment.

	At entry[1] (n=28)	After treatment[1] (n=28)	P-value
Body weight (kg)	50	52.5	<0.0001
Body mass index (kg/m^2)	19	19.5	<0.0001
Albumin (g/dl)	3.0	3.4	<0.0001
White blood cell count (/mm^3)	10,400	8,000	<0.0001
Platelet count (/mm^3)	520,000	310,000	<0.0001
Erythrocyte sedimentation rate (mm/hr)	48	23	<0.0001
C-reactive protein (mg/dl)	4.7	1.0	<0.0001

[1] Median values are presented.

21.9.2. Maintenance therapy for quiescent disease

After achieving clinical remission, patients receive half ED therapy at their homes: approximately half of the calories are taken from ED (Figure 21.1). A thin (external diameter, 1.7 mm), soft silicone-elastomer nasogastric tube is self-intubated every night, and the ED is infused continuously through the tube using an infusion pump during the nighttime. In the daytime, low fat foods are taken. According to instructions given by dieticians, patients are advised to take a total of 35-40 kcal/kg ideal body weight/day, and to take approximately half of the energy from the ED. Our nutritional support team regularly interview the patients to ensure that adherence to their assigned regimen is according to the protocol.

In a recent prospective study, we evaluated the efficacy of half ED therapy for patients with quiescent CD (Yamamoto *et al.,* 2007a). 40 consecutive patients (27 males and 13 females; mean age, 30 years) were studied. The mean duration from the diagnosis of CD to entry was 34 months. The location of CD was in the terminal ileum (including neo-terminal ileum after resection) alone in 15 patients, in the colon alone in four patients, and in both the terminal ileum and the colon in 21 patients. Prior to the present study, during active CD, the mean CDAI score was 325 (range, 255-425). Patients were treated with PSL and infliximab in four patients; PSL with EN in six patients; PSL alone in 10 patients; and EN alone in 20 patients. All patients achieved clinical remission (CDAI<150). The mean CDAI score at entry was 97 (range, 56-139). Before entry, all patients had experienced ED infusion through a self-intubated nasogastric tube using an infusion pump. In each patient, compliance with the treatment was assessed by both physicians and nutrition staff. Twenty patients with good compliance could insert the nasogastric tube without any difficulties, and had no serious abdominal symptoms during the infusion of the ED. In contrast, the other 20 patients with poor compliance could not insert the nasogastric tube by themselves, or developed serious abdominal distension and diarrhoea during infusion of the ED. The 20 patients with good compliance were assigned to EN-group, and the 20 with poor

compliance were assigned to non-EN group. In the EN group, patients were treated with the above-mentioned half ED therapy (Figure 21.3). The volume of the ED infused per night (over 6-10 hr) was 1,200-1,800 ml. In the daytime, low fat foods (20-30 g/day) were taken in accord with instructions of their dieticians. In contrast, patients in the non-EN group had neither any nutritional therapy nor any food restriction during the entire study time. With these regimens, all 40 patients were monitored for one year. Further, ileocolonoscopy was performed at entry, at 6 and 12 months and mucosal biopsies were taken for cytokine assays. The endoscopic severity of mucosal inflammation was graded as follows (Wardle *et al.,* 1992): score 0, macroscopically normal; score 1, granular mucosa and contact bleeding; score 2, erythematous and edematous mucosa, aphtoid or superficial ulcers; and score 3, presence of deep ulcers with slough and inflammatory pseudopolyps.

At entry, patients in both treatment groups were well matched with respect to age, gender, duration of CD before entry, smoking history, previous bowel operation, disease location, the CDAI score, and nutritional status. In the EN group, most patients experienced diarrhoea, or abdominal distension or colic during the ED infusion during the treatment. The symptoms were not serious, and receded by temporary decreases in the infusion rate without interruption of the treatment. However, two patients could not continue tube incubation for ED infusion. Except the two patients, all could continue with their EN therapy for one year.

During the one year study time, the rate of clinical relapse (CDAI≥150) was significantly lower in the EN group (25%) than in the non-EN group (65%). Similarly, the cumulative relapse rate was significantly lower in the EN group. The mean endoscopic scores were not significantly different between the groups at both entry and 6 months, but at 12 months, the scores were significantly lower in the EN group (Figure 21.4). Additionally, the mucosal tissue IL-1β, IL-6 and TNF-α levels significantly increased with time in the non-EN group. However, in the EN group, these cytokines did not show a significant increase. There were significantly higher intakes of energy, protein, and carbohydrate in the EN group (enteral formula *plus* foods) as compared with the non-EN group (Figure 21.5). In contrast, there was a significantly higher intake of fats (Figure 21.5). The body weight, BMI and serum albumin level gradually increased with time in the EN group. In contrast, these values began to decrease at four or six months in the non-EN group. The outcomes of this study suggest that one-year half ED therapy for patients with quiescent CD has a
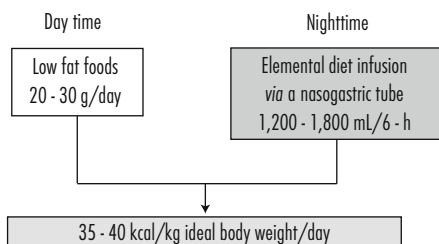
Figure 21.3. Half elemental diet therapy for patients with quiescent Crohn's disease.
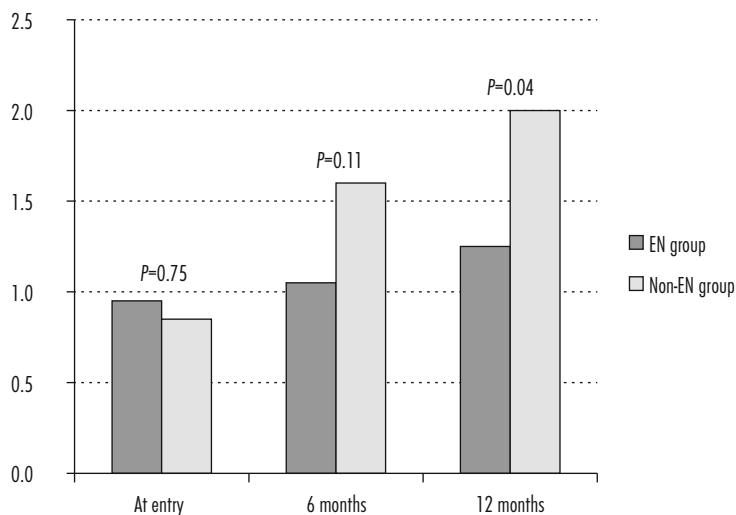
Figure 21.4. Comparisons of the endoscopic scores between patients treated with and without half elemental diet therapy.
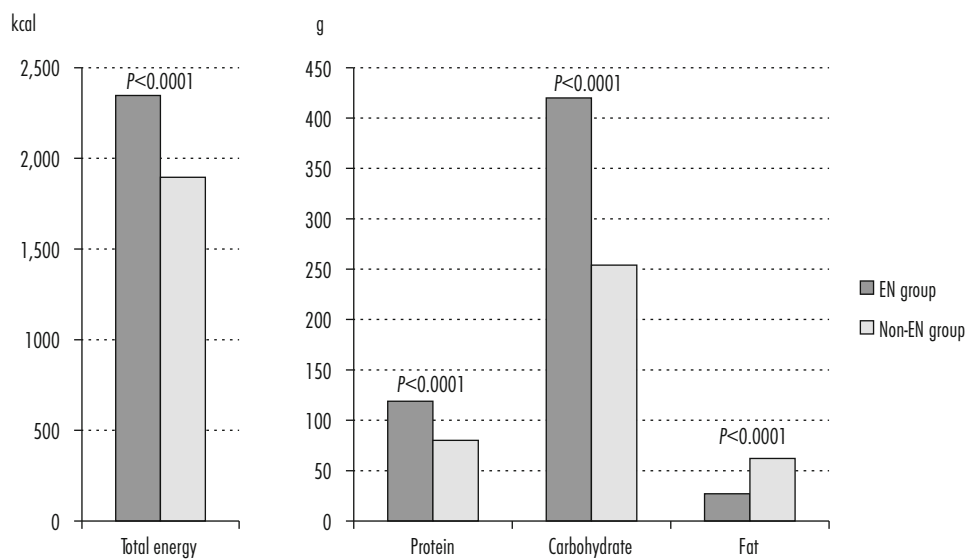
Figure 21.5. Comparisons of daily intake of total energy, protein, carbohydrate and fat between patients treated with and without half elemental diet therapy. Mean values are presented.

clear suppressive effect on clinical and endoscopic disease activity, and the mucosal inflammatory cytokine levels. Furthermore, this ED therapy maintains a favourable nutritional status in the long-term. Long-term half ED therapy might be a workable strategy to maintain remission of CD.

21.9.3. Maintenance therapy following surgery

We also evaluated the efficacy of the above-mentioned half ED therapy in preventing recurrence after surgery for CD. In our prospective trial, 40 consecutive patients (26 males and 14 females; mean age, 32 years) who underwent resection for ileal or ileocolonic CD were studied (Yamamoto *et al.,* 2007b). The mean duration from diagnosis of CD to operation was 38 months. After operation, 20 patients continuously received half ED therapy following surgery (EN group), and 20 had neither nutritional therapy nor food restriction (non-EN group). All patients were followed up regularly for one year after surgery. Ileocolonoscopy was performed at 6 and 12 months after surgery.

During one-year follow-up, the rate of clinical recurrence (CDAI≥150) was significantly lower in the EN group (5%) than in the non-EN group (35%). At 6 months after operation, 5 patients (25%) in the EN group and 8 (40%) in the non-EN group developed endoscopic recurrence (not significant). At 12 months after operation, endoscopic recurrence was observed in 6 patients (30%) in the EN group and 14 (70%) in the non-EN group, with the difference being significant. The results of this study may indicate that one-year half ED therapy reduces clinical and endoscopic recurrence after surgery for CD.

21.10 Discussion

In our studies (Yamamoto *et al.,* 2005, 2007a, 2007b), we evaluated the efficacy of EN therapy with nocturnal enteral support. Patients with acute CD were treated by exclusive ED therapy: continuous ED infusion through a nasogastric tube. Four-week exclusive ED therapy achieved clinical and endoscopic remission in the majority of patients with mild-to-moderate active CD. This treatment also reduced the mucosal cytokine production and corrected an imbalance between pro-inflammatory and anti-inflammatory cytokines. After achieving clinical remission (including postoperative conditions), patients with quiescent CD were treated with half ED therapy for prevention of relapse or recurrence. A nasogastric tube was self-intubated every night, and the ED was infused continuously through the tube using an infusion pump during the nighttime. In the daytime, low fat foods were taken. One-year half ED therapy with nocturnal feeding showed a clear suppressive effect on clinical and endoscopic disease activity, and the mucosal inflammatory cytokine production in patients with quiescent CD.

During enteral support at sleep time, none of our patients experienced serious problems, and this procedure did not disturb sleep. All patients could continue nocturnal infusion of the ED in the long-term. In the maintenance therapy for quiescent disease (Yamamoto *et al.,* 2007a), there were significantly higher intakes of energy, protein and carbohydrate, and significantly lower intakes of fats in patients with half ED therapy. Long-term half ED therapy was helpful in maintaining a

favourable nutritional status. In our experience, it is difficult for patients with CD to take enough calories during the daytime to maintain good physical health and well-being. Many patients are intolerant to oral intake of large amounts of diets, but tube feeding during the daytime is practically impossible in everyday life. With this in mind, nocturnal enteral feeding is helpful for patients to take enough calories to maintain a good health and satisfactory nutritional status. The author does not have striking evidence supporting nocturnal EN therapy in the management of patients with CD. To our knowledge, there have been no clinical studies comparing the efficacy of EN with and without nocturnal enteral support. Furthermore, there has been no research to show how nocturnal enteral feeding works in patients with CD. Although further studies are necessary, the outcomes of our clinical trials suggest that EN therapy with nocturnal enteral support is useful in inducing and maintaining clinical remission, and in improving nutritional status of patients in the long-term.

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Foods and nutrients and other factors that disturb sleep

Summary points

- The relationship between caffeine and sleep is a complex one.
- Whilst studies comparing caffeine and placebo seem to demonstrate a relationship between caffeine and an inability to get to sleep, we may also be observing an increase in sleepiness caused by caffeine withdrawal.
- The cessation of caffeine a number of hours before bedtime, observed by many, may be a behaviour learnt over time by consumers in order to maximise sleep.
- Tolerance may be built up over time.
- Some consumers may be more sensitive to caffeine and its effects on sleep than others.
- Dose and habitual consumption may play an important role in sensitivity towards caffeine.
- Physiological symptoms of caffeine may be somewhat responsible for sleepiness which includes tremor and jitteriness. In addition these symptoms are likely to be proportional to the quantity of caffeine consumed and may vary with tolerance and sensitivity.

22. Caffeine, sleep and sleepiness: withdrawal, dependence and tolerance

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Abstract

As a well known, and consumed, psychostimulant, caffeine has long been associated with sleep disruption. As such it has been advocated for use in keeping shift workers and sleepy drivers alert. However, in the last decade or so evidence has grown to suggest that the alerting effects of caffeine are merely the restoration of normal functioning following a period of caffeine abstinence. It may, therefore, be a futile remedy to sleepiness. Additionally, caffeine is also thought to disrupt sleep with sleep hygiene advice advocating the cessation of caffeine consumption prior to bedtime. However, responses to caffeine at bedtime are variable and studies are possibly confounded by withdrawal. The effect of caffeine on sleep and alertness will be discussed in relation to habitual consumption, withdrawal and tolerance.

Keywords: consumption, alertness, shift work, driving, health

Abbreviations

ONW   Overnight withdrawn
LTW   Long-term withdrawn

22.1 Caffeine

With an estimated 80% of the world's population consuming it daily (James, 1997), caffeine is the world's most popular drug. Consumption is mainly through its naturally occurring form found in tea and coffee (Table 22.1) and to a much lesser extent chocolate. However, it can also be found as an additive to cola, energy drinks, and some medication. Europeans are known to consume around 200-300 mg per day (Barone and Roberts, 1996; Heatherley *et al.*, 2006).

22.1.1 Caffeine's action in the brain

Caffeine is one of a group of methylated xanthines known as trimethylxanthine whose action is based on the central nervous system. The effects of caffeine occur via antagonism of the neuromodulator adenosine at adenosine A_1 and A_{2A} receptors (Freedholm *et al.,* 1999). These receptors are distributed throughout the body and by blocking the action of adenosine, caffeine has significant cerebrovascular, cardiovascular, renal, gastrointestinal and metabolic effects. A_1 and A_{2A} receptors are involved in the regulation of sleep, wakefulness, arousal and cognition as well as some mood disorders such as anxiety (Rogers *et al.,* 2010). Caffeine consumption causes vasoconstriction, however, following cessation of caffeine vasodilation occurs increasing blood flow often leading to headache. Regular use of caffeine may result in an increased number of adenosine receptors resulting in hypersensitivity to adenosine after abrupt cessation of the drug.

Table 22.1. Summary of estimates of the caffeine content of beverages (The Food Standards Agency and manufacturer's information; Heatherley *et al.,* 2006, adapted with permission. Copyright 2006 by Elsevier).

Caffeine product	Caffeine in mg per glass, cup, can, etc.
Instant coffee	54
Ground coffee	105
Tea (loose, bag, instant and green)	40
Branded cola	30
Own brand cola	16
Energy drinks	80

22.1.2 Caffeine withdrawal

It is well-known that caffeine acts as a stimulant. In laboratories it has been shown to improve reaction time, alertness and energetic mood (Haskell *et al.,* 2005; Heatherley *et al.,* 2005; Smit and Rogers, 2000). In addition, it has been claimed to assist sleepy drivers stay awake behind the wheel (Horne and Reyner, 2001) and night shift workers alert (Schweitzer *et al.,* 2006; Walsh *et al.,* 1990).

For a long time it was assumed that these alerting effects of caffeine were due to a net benefit of the drug; that is, caffeine is a stimulant which, when consumed, improves mood and mental performance. However, James (1994) and Rogers *et al.* (1995) suggested that researchers were being misled. James revealed that caffeine experiments had the major flaw of testing habitual caffeine consumers after they had abstained from caffeine overnight. Participants would be tested having been told to avoid all caffeine for at least 8 hrs (understandably not to confound the test caffeine with any dietary caffeine the participants may normally consume). Following caffeine treatment or placebo, participants' mood and performance would be measured again. Participants given caffeine would demonstrate an improvement in performance compared with baseline and/ or post treatment placebo performance. However, James argued that participants' performance at baseline was actually impaired by caffeine withdrawal and the improvements post treatment were merely restoring performance to a baseline level rather than improving performance above and beyond a normal level of functioning. The symptoms of caffeine withdrawal, responsible for the decline in performance, include headache, tiredness/fatigue and decreased alertness (Juliano and Griffiths, 2004).

In contrast, there are several authors who maintain the view that caffeine provides a net benefit to its consumers. Smith (2002) argues that the withdrawal theory cannot account for the behavioural effects seen in non-consumers where withdrawal cannot occur. Effects of caffeine on non-consumers or low consumers have been reported (Smith *et al.*, 2006; Childs and De Wit, 2006). On the other hand, Rogers *et al.* (2003) found no effect of caffeine in their low consumers. Haskell *et al.* (2005) compared caffeine consumers and non-consumers and found no baseline differences in the performance of the two groups with both groups demonstrating increased alertness and improvements in performance following caffeine administration. However, Haskell *et al.* may have underestimated the amount of caffeine consumed by their non-consumers as their systemic level of caffeine following 12 hrs of abstinence was similar to their consumers' levels (0.36 and 0.50 and microgram/ml respectively). In comparison, in a recent study by Rogers *et al.* (2012), low/non consumer salivary caffeine concentration was found to be only 0.02 microgram/ml.

Experiments with non or low consumers can be confounded not only by individual's understanding of their own caffeine consumption, but also by a variation in response to caffeine. One argument often used against comparing non-consumers with consumers is that non-consumers are a self-selected group. James (1998) argues that the most controlled way to test caffeine withdrawal is to expose the same participants to a number of run-in days (either caffeine maintained or placebo maintained) followed by a caffeine or placebo challenge day. Therefore, overnight and long-term

withdrawn participants are tested on the acute effects of caffeine or placebo on a challenge day (Table 22.2). This, or similar methods have been used on a number of occasions and the results have supported the withdrawal hypothesis (James and Gregg, 2004; Yeomans *et al.,* 2002; Rogers *et al.,* 2005).

Consequently, the withdrawal hypothesis predicts that:
- ONW consumers will perform worse than non-consumers or LTW consumers at baseline as demonstrated by their slower reaction times;
- following caffeine administration, there will be no change in the performance of the LTW consumers;
- following caffeine administration, the performance of the ONW consumers will improve as performance is restored following withdrawal decrements, but only to the baseline level (or similar) of the LTW consumers;
- ONW consumers who receive placebo will continue to perform worse than the LTW with increasing withdrawal symptoms (e.g. headache).

Figure 22.1 demonstrates the effect of overnight caffeine abstinence on driving performance when compared with long-term caffeine abstinent consumers. The long-term abstinent consumers have abstained from caffeine for 2 weeks. The performance of the ONW participants is impaired with consistently more lane error drifts in comparison with the LTW. The symptoms of caffeine withdrawal such as fatigue, sleepiness, lowered alertness and headache contribute to a lowering of mood and performance. As these symptoms can be reversed by the administration of caffeine, the

Table 22.2. Summary of a double-blind placebo-controlled crossover protocol incorporating alternating periods of 'long-term' caffeine exposure and abstinence (James and Keane, 2007, reprinted with permission. Copyright 2007 by John Wiley & Sons Ltd.).

Week	Run-in days (days 1-6)	'Challenge' (day 7)	Condition	Effects revealed by challenge
1	placebo	placebo	PP	sustained abstinence (i.e. caffeine 'wash out'): serves as a caffeine-free baseline
2	placebo	caffeine	PC	acute challenge: when compared to PP and CC, reveals the presence of tolerance
3	caffeine	placebo	CP	acute abstinence: when compared to PP and CC, reveals the presence of withdrawal
4	caffeine	caffeine	CC	habitual use: when compared to PP, reveals the net effects of habitual consumption

PP = placebo ingested for 6 consecutive days followed by 1 day of placebo challenge; PC = 6 days of placebo followed by 1 day of caffeine challenge; CP = 6 days of caffeine followed by 1 day of placebo challenge; CC = 6 days of caffeine followed by 1 day of caffeine challenge.
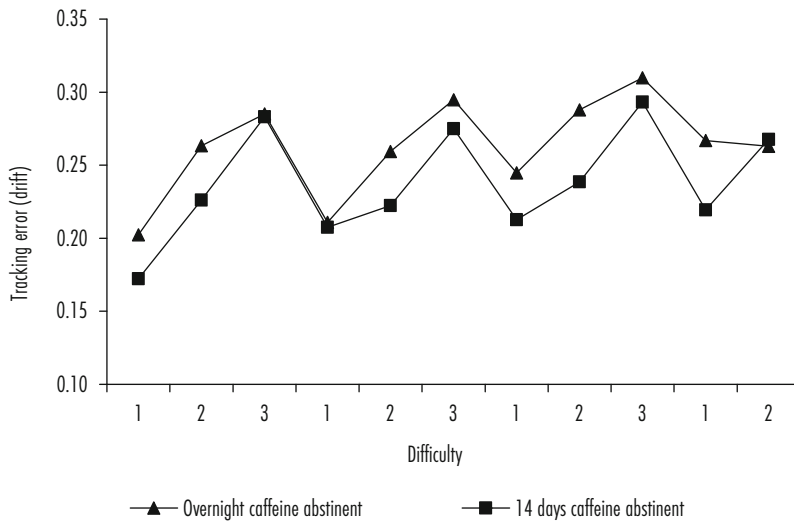
Figure 22.1. Tracking error in overnight and 14 day caffeine abstinent drivers during a 30 minute drive of a lap containing 3 levels of difficulty, 1 being the easiest (Heatherley, 2011, reprinted with permission. Copyright 2011 W.S. Maney&Son Ltd.).

possibility of misattributing caffeine with the ability to combat sleepiness is common. Therefore, when measuring the effects of caffeine on variables such as sleepiness, studies need to allow for the confounding effects of withdrawal.

22.2 Caffeine as a drug for combating sleepiness: shift work, jet lag and driving

A normal sleep/wake cycle is determind by an endogenous circadian rhythm which affects body temperature, hornmone secretion, sleep and alertness (Rea *et al.,* 2008). This, along with exogenous cues or *zeitgebers* such as light, results in a strong propensity to sleep between the hours of 01:00 and 08:00 (Richardson *et al.*, 1982). Whilst most of us give in easily to this propensity (being in bed for at least most of this time), for many, such as medical workers or air crew, staying awake and alert during this period is essential. Additonally, shift work has increased considerably over the years due to the modern propensity for a 24 hr existence, a lack of employment options and the benefits in compensation (e.g. time in lieu) for working unsociable hours (HSE, 2006). Consequently, in the UK around 14% of the work force do shift work (HSE, 2006). Circadian rhthym sleep disorders are prevalent in these occupations as normal sleep routines (governed by circadian rhthyms) are forced into a different pattern.

For many shiftworkers remaining alert at work when sleepy is a serious problem. Errors caused by sleepiness can results in serious harm or fatalities. It has been estimated that between 44,000

and 98,000 deaths in the US every year are caused by medical error (Kohn *et al.,* 1999) and in the UK at least 850,000 incidents involving National Health Service patients every year. Similarly, piloting errors during longhaul flights crossing several time zones can be critical. With caffeine a potential stimulant to assist in keeping sleepy individuals awake, it has been used in a number of trials to combat sleepiness for example: military operations (McLellan *et al.,* 2005) and shift work (Muehlbach and Walsh, 1995).

Driver sleepiness has been held responsible for 20-25% of motorway accidents in the UK (Horne and Reyner, 1995), around 10% of serious road crashes in France (Philip *et al.*, 2001) and 1-3% of all US motor vehicle crashes (James, 1998). Studies claiming that caffeine can improve performance in sleepy drivers has led to the use of caffeine to overcome sleepiness with advice given to stop and 'take drinks containing caffeine' (ROSPA, 2001). Reyner and Horne (2000) studied the efficacy of 200 mg of caffeine on eight sleep restricted and eight totally sleep deprived drivers early in the morning. Participants received either caffeine or placebo before commencing a 2 hr drive 30 min later. After only 5 hrs sleep, the participants who received caffeine experienced fewer driving incidents than the placebo group and the number of incidents remained consistently low until the final half hour of the drive. Contrastingly, the placebo group's incidents increased in a linear trend. However, the participants in this study were all caffeine consumers who had been asked to abstain from caffeine overnight. Therefore, the effects of caffeine are quite likely due to withdrawal reversal. This pattern of results is also consistent with other caffeine studies where performance in the placebo group gradually declines during the course of the study due to increasing withdrawal symptoms such as sleepiness and headache (Figure 22.2). In the second part of the study, caffeine had little effect on total sleep deprivation. Although it reduced the number of incidents compared with the placebo group during the first 30 min of the drive, the study was abandoned after one
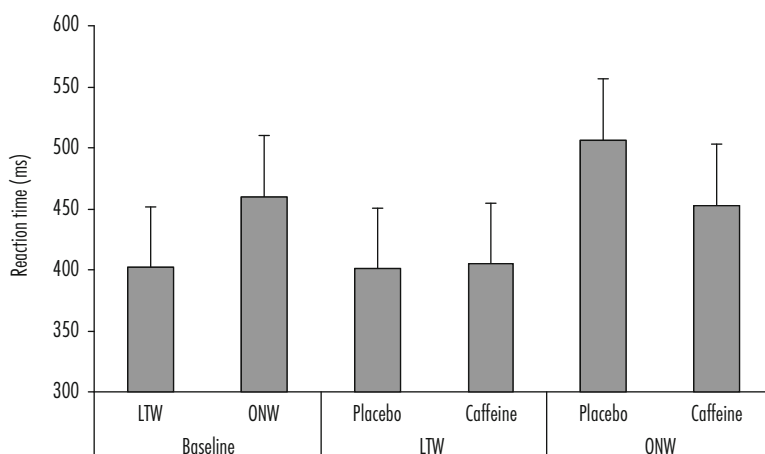
Figure 22.2. Reaction time of long-term withdrawn (LTW) versus overnight withdrawn (ONW) participants before (baseline) and after placebo or caffeine challenge following sleep restriction to 5 hrs (Rogers *et al.*, 2005, adapted with permission. Copyright 2005 by Springer-Verlag).

hour due to the extremely poor performance of both groups. For a full review of driving and caffeine studies see Heatherley (2011).

What seems to be commonplace in many studies, including serveral pivotal driving studies, is the acknowlegement of the existence of caffeine withdrawal followed by a denial that it would happen within that study due to the level of caffeine consumed by the participants. This raises a number of issues:

- Unless beverages are carefully studied '2 coffees a day', used as a benchmark for consumers in several studies, can have as much as 250 mg of caffeine or more.
- Even low doses of caffeine (100 mg or less), if regularly consumed, can cause withdrawal symptoms when consumption ceases (James, 1997).
- If avoidance of withdrawal was the aim of the investigators, then why not use long-term caffeine abstinent consumers?
- With the general population of the UK and Europe consuming around 200-270 mg of caffeine a day it seems reasonable to represent this group of consumers rather than try to recruit a minority that consume less.

The results presented in Figure 22.2 (Rogers *et al.,* 2005) demonstrate caffeine withdrawal effects following two different states of caffeine abstinence. In this particular study the participants were moderate caffeine consumers either overnight withdrawn, or long-term withdrawn. A battery of cognitive tasks were given before and after caffeine or placebo treatment following sleep restriction of 5 hrs (a reduction of around 3 hrs sleep for the participants). Crucially, though, one group (LTW) had unknowingly consumed decaffeinated drinks for 3 weeks prior to the challenge day.

Even in a state of low alertness induced by sleep restriction, caffeine did not benefit performance in the long-term withdrawn participants. The overnight withdrawn participants performed worse at baseline in comparison with the long-term withdrawn particiants as expected, and caffeine affected performance in the former, but not the latter group.

Despite these findings, individuals will continue to attempt to use caffeine to keep awake during challenging working hours. However, apart from any real evidence to demonstrate its success, undesirable side-effects of caffeine should be considered. Caffeine is generally avoided too close to bedtime as it may interfere with sleep. Following a night shift or similar working hours individuals are likely to want to get to sleep as quickly as possible to maximise the number of daylight hours they may be awake for and to be properly refreshed before another shift. However, if caffeine has been consumed near to bedtime in order to keep the individual awake during working hours, it will possibly have a disruptive effect on sleep (Jay *et al.,* 2006).

Long-term exposure to shift work has been associated with cardiovascular problems such as hypertension and coronary heart disease (HSE, 2006). Additionally, there is increasing evidence that caffeine has a negative effect on blood pressure and, therefore, is a potential risk factor in cadiovascular disease (James, 2004; Lane *et al.,* 1990).

Apart from the fatiguing effects of caffeine withdrawal, caffeine has acute negative effects such as increased jitteriness (Juliano and Griffiths, 2004) and increased hand tremor (Heatherley *et al.,* 2005; Rogers *et al.,* 2005). These symptoms may be particularly prominent with high doses of caffeine. These side-effects would be highly undesirable when operating machinery, or jobs requiring precision or manual dexterity such as those in the medical profession. Figure 22.3 demonstrates the effect of caffeine on hand steadiness. When there is a gap of 8 hrs before the dose of caffeine, hand steadiness has been little affected. However, the shorter gaps, especially 4 hrs have increased systemic levels of caffeine causing hand steadiness to decrease and the number of contacts, therefore, to increase.

Anxiety and stress are additional side effects of caffeine consumption. Caffeine has been found to induce anxiety in individuals carrying certain genotypes of the adenosine A2A receptor gene (Alsene *et al.,* 2003), although more frequent consumption of caffeine may lead to chronic tolerance (Rogers *et al.,* 2010). However, having a sensitivity to caffeine and anxiety does not seem to alter consumption. In contrast, Lane *et al.* (1990) demonstrated that caffeine can increase cardiovascular and neuroendocrine stress reactivity elicited by psychosocial stressors and these responses did not seem to be affected by habitual consumption.

Caffeine is not an ideal drug for keeping sleepy individuals wakeful at work, because:
- it is quite likely ineffective in the abscence of caffeine withdrawal;
- starting and stopping consumption can lead to undesirable side-effects of caffeine withdrawal
- high and continued use can contribute towards health risks and side effects which could impact on work safety;
- as caffeine may interfere with sleep, losing additional important hours of sleep for shift workers can increase work errors as well as being detrimental to health.
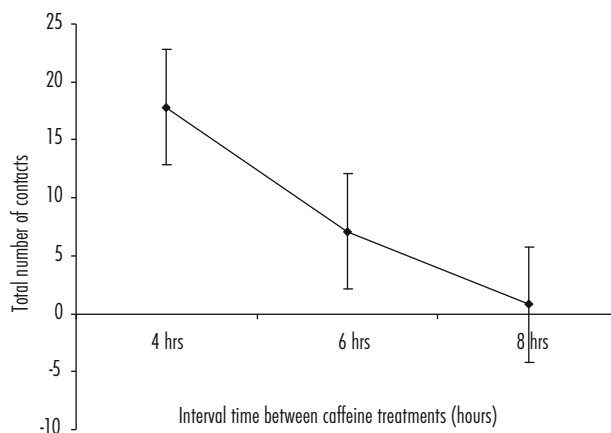
Figure 22.3. Effects of caffeine (1.2 mg/kg) on hand steadiness after a period of caffeine abstinence of 4, 6 and 8 hrs (Heatherley *et al.,* 2005, reprinted with permission. Copyright 2005 by Springer-Verlag).

22.3 Caffeine and sleep

When sleep hygiene advice is given, avoidance of caffeine prior to bedtime is most frequently included. Studies have demonstrated that high doses of caffeine taken before bedtime will delay sleep onset in many individuals and consequently most people control their daily consumption to avoid caffeine at this time (Rogers *et al.,* 2003). However, individual responses to caffeine are varied and may be dependent on a number of factors such as total daily consumption, pattern of consumption, individual metabolic responses to caffeine and tolerance to the drug. Whilst it seems unequivocal that caffeine interferes with sleep, for some individuals this may not be the case. For example, Sanchez-Ortuno *et al.* (2004) found no relationship between total sleep time and daily caffeine intake up to the equivalent of 7 cups of coffee per day (680 mg of caffeine) in a survey of nearly 1,500 middle-aged workers based on 3 weeks' of observations. It may be that up to 7 cups can be consumed early enough in the day not to effect sleep, but larger amounts are consumed over a longer period and, therefore, closer to bedtime. An unusal finding was that time in bed was reduced as caffeine intake increased resulting in an increase in sleep efficiency. This may be because higher caffeine users wait longer before going to bed to avoid long periods of wakefulness, or a tolerance has been built up with consumers who may not be sensitive to caffeine, or that these individuals are awake longer in the day due to busy schedules.

In contrast, Pollack and Bright (2003) found that teenagers were more susceptable to the effects of caffeine on sleep. Whilst consuming an average of only 52.7 mg/per day, caffeine consumption was associated with more waking in the night and higher users had more disturbed sleep on nights after increased caffeine use. Pollack and Bright also found that caffeine consumption increased from Wednesday indicating that maybe students were trying to counteract daytime sleepiness caused by sleep deprivation on school nights. It is common for students to use caffeine in an attempt to stay awake whilst studying for assignments and exams. However, this may be counter-productive as caffeine may increase preexisting feelings of stress (Lane *et al.,* 1990) and impact on later sleep as suggested in this study.

What is evident from these two studies is that while the students demonstrate little tolerance to caffeine, the middle-aged consumers seem to have a strong tolerance. This may be due to:
- the middle-aged population having a higher, but very regular pattern of consumption in comparison with the students;
- the middle-aged population managing their consumption according to sleep (avoiding consumption late in the evening);
- a tolerance being built up over a long period of time.

It may also be that caffeine disrupts sleep in individuals with a habitually low level of consumption when consumed in higher doses. The participants in Sanchez-Ortuno's study were regular coffee drinkers whereas Pollack and Bright's teenagers obtained their caffeine from 'sodas'.

In another study, Hindmarch *et al.* (2000) compared the effects of several doses of low and high tea and coffee consumption with water across a day on the effects of cognitive performance and sleep.

Participants in this study were caffeine consumers and had been told to abstain from caffeine from 10 pm the previous evening. In comparison with water, caffeine had a detrimental effect on both perceived and actual sleep. Whilst withdrawal would be an obvious explanation for these effects with the water group having been free of caffeine for 24 hrs, total sleep time was dose dependent with increasing levels of caffeine resulting in shorter sleep. This is in contrast to performance where no dose-response relationship was found. This is consistent with other withdrawal studies measuring cognitive performance where there is a flat dose-response relationship to caffeine (Heatherley *et al.*, 2005). In addition, Hindmarch *et al.* (2000) found the effect of caffeine on sleep was affected by habitual intake with the lowest consumers sleep being disrupted the most. This may be due to higher consumption leading to increased tolerance, or lower consumers limiting their consumption due to a higher sensitivity to caffeine (Hindmarch *et al.,* 2000).

It is, however, likely that withdrawal increases sleep onset. Walsh *et al.* (1990) studied the effects of 4 mg/kg body weight of caffeine versus placebo taken around 10:30 pm on young adults (either mild or moderate caffeine users) in both falling asleep and staying awake during the night. Caffeine, in comparison to placebo increased sleep latency and increased sustained wakefullness. However, both groups had abstained from caffeine for around 9 hrs prior to the study. Therefore, the caffeine group would most likely be feeling an initial increase in alertness following the reversal of caffeine withdrawal symptoms (Figure 22.4). In fact whilst sleep latency decreases throughout the night (measures were taken several times during the night), the biggest difference for the caffeine group is from 4 to 6 hrs post caffeine. This is consistent with the onset
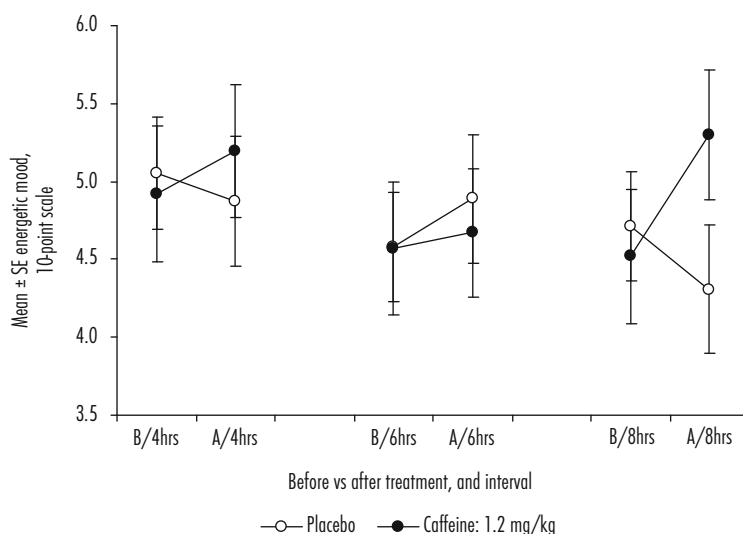
Figure 22.4. Effects of caffeine on energetic mood after 4, 6 and 8 hrs prior caffeine abstinence. The data show self-rated energetic mood (B) before and (A) after treatment with placebo or caffeine. There was only a significant effect of caffeine in the 8 hr abstinent group ($P<0.01$) (Heatherley *et al.,* 2005, reprinted with permission. Copyright 2005 by Springer-Verlag).

of caffeine withdrawal symptoms which usually starts around 6-8 hrs post caffeine consumption when systemic levels of caffeine have fallen sufficiently low in line with caffeine's half-life which is around 3 to 7 hrs (Heatherley *et al.*, 2005). The placebo group latency always remained lower, but again this is consistent with withdrawal as symptoms may begin at 6 hrs abstinence and peak at aound 24 hrs (James, 1997). There was also no difference between results of the mild or moderate caffeine consumers.

22.4 Conclusions

It is important that future experiments control for caffeine withdrawal use designs which test both long-term withdrawn and overnight withdrawn individuals with varying levels of habitual consumption. Objective measures need to be made to test individual sensitivities to this most popular drug.

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Summary points

- The length of a night's sleep in 'healthy' individuals has shortened from 1972-1985 by 18 minutes.
- The risk of death increased by more than 15% in those reporting more than 8.5 or less than 3-5-4.5 hrs sleep per night.
- It is commonly believed that alcohol will help an individual to sleep.
- Whilst alcohol is a sedative, tolerance to these effects is usually developed within three days.
- A phenomenon known as 'REM rebound' (REM=rapid eye movement; linked to intensive dreams or nightmares) has been reported, that is associated with alcohol having been metabolised often in the early hours of the morning. The severity of 'REM rebound' is dose-related.
- The link between alcohol and the time taken to fall asleep is unpredictable and dependent upon dosage and length of time between consuming alcohol and attempting to sleep.
- Alcohol taken at bedtime has a paradoxical stimulating effect.
- Much of the literature considers alcohol and sleep in healthy individuals in combination with socio demographic factors such as, obesity, diet, cigarette smoking, mental and physical health status.
- Tolerance to the sedative effects of alcohol is established within 3-7 days.
- Alcohol diminishes the quality of sleep.
- Alcohol is linked to obstructive sleep apnoea (OSA) because it relaxes upper airway dilator muscles.

23. Alcohol and sleep

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Abstract

Alcohol has sedative properties and there is a link with sleep, but the research concerning the impact of alcohol on 'healthy' individuals has gone into comparative abeyance. There is continuing work but most of it considers alcohol in combination with cigarettes, obesity, diet, mental and physical health. Epidemiological data show that the average night's sleep has shortened by around 20 minutes and this has been put down to increasingly stressful lifestyles, longer working hours and night time television. Alcohol is often used as a sedative but tolerance is developed within 3-7 days. Alcohol taken late at night affects the quality of sleep and this is particularly the case when alcohol is metabolised and has left the brain and body. Finally the link between alcohol and insomnia and obstructive sleep apnoea (OSA) and traffic accidents is discussed. The research confirms a link between alcohol-related mortality and mortality in both of these conditions. Again the main impact of alcohol is to affect the quality of sleep. It is however difficult to make firm conclusions concerning the relationship between alcohol and OSA because it is often considered in combination with smoking, obesity, and mental/physical health. Finally a call is made for more research that allows the impact of alcohol to be assessed independent of other factors.

Keywords: alcohol, sleep, insomnia, obstructive sleep apnoea, driving performance

Abbreviations

NRS	Non- restorative sleep.
OSA	Obstructive sleep apnoea
OTC	Over the counter
PSD	Partially sleep deprived
PSD+ A	Partially sleep deprived + alcohol
PSG	Polysomnography
REM	Rapid eye movement (sleep)
SWS	Slow wave sleep

23.1 Introduction

This chapter will consider some of the international research findings examining the link between alcohol and sleep in non-alcohol dependent individuals. The emphasis will be upon 'healthy' individuals but at times studies will be quoted that consider the link between alcohol and alcohol abuse.

23.2 Sleep in the general population: some epidemiological findings

The National Health Institute Survey (Schoenberg and Adams, 2008) estimated that over 70 million Americans are affected by chronic sleep loss and sleep disorders. The optimum sleep duration for the maintenance of good health is 7-8 hrs (Bixler, 2009) and both less and greater than this is associated with increased morbidity (Gangswisch *et al.,* 2007) and mortality (Hublin *et al.,* 2007). The 1982 Cancer Prevention Study II (US) showed an important link between diminished and excessive sleep. The risk of death was increased by more than 15% in those reporting more than 8.5 or less than 3-5-4.5 hrs sleep per night (Kripke *et al.,* 2002).

There is a trend towards less sleep in the general population, and a Finnish study has shown that from 1972-2005 mean sleep duration had reduced by 18 minutes and this was accompanied by an increase in sleep disturbance in middle age males (Kronholm *et al.,* 2008). Over the past 50 years sleep duration has reduced in US adults and adolescents by 1.5 hrs (Cauter *et al.,* 2008). The reasons for these changes are unclear but possible explanations include late night television, greater use of the internet and longer working hours (Bixler, 2009). It is likely that socioeconomic factors are associated with these changes for ethnicity, income and lower educational status are linked to less sleep.

This chapter will focus upon the relationship between alcohol and sleep but at this point it is important to note that much research has considered it alongside smoking, obesity and lack of exercise. In combination these are associated with less than 6 hrs or greater than 9 hrs sleep per night (Schoenberg and Adams, 2008). However the relationship between these and

sociodemographic factors such as poverty low economic status needs further investigation. The Wisconsin Sleep Cohort (Taheri *et al.,* 2004) and Penn State Cohort studies (Vgontzas *et al.,* 2008) suggest that obesity is the strongest factor as it is constant across gender, age and ethnic grouping.

The National Sleep Foundation (2001) suggested that the trend towards less sleep has been accompanied by greater stress. Individuals who slept for less than 7 hrs or more than 8 hrs sleep reported difficulty falling asleep, waking during the night, waking too early and day time sleepiness.

23.3 Effects of alcohol on sleep

Alcohol is frequently taken under the belief that it will aid sleep. The sleep stages are result of interactions between two chemicals in the lower brain stem. These are firstly serotonin, linked to sleep onset and the regulation of SWS and secondly norepinephrine which regulates REM sleep and encourages arousal. However the mechanisms of these interactions are unclear. A healthy individual aged 20 years will have a typical sleep latency of 10 minutes or less, 95% sleep efficiency (percentage of time spent asleep as compared with time in bed), few episodes of night time awakening and a smooth progression through the sleep stages (Vitiello, 1997). When consumed in the early evening the sedative effects of alcohol on REM sleep, slow wave sleep, sleep time and continuity are predictable but the impact on sleep latency (the time to fall asleep) are more varied (Stein and Freedman, 2005).

Alcohol inhibits REM sleep at high doses (1 g) in healthy subjects within an hour of sleeping, but the effects are less predictable at doses below 1 g. A phenomenon known as 'REM rebound' (Roehrs and Roth, 2001) which is associated with intensive dreams or nightmares occurs on cessation of drinking or when the body has metabolised the amount of alcohol consumed.

SWS increases after high to moderate bedtime alcohol use but again the results are less consistent at smaller doses. Furthermore the impact on SWS is lessened with repeated nights of alcohol consumption.

The impact of alcohol in sleep continuity and total sleep are both variable and seemingly dose related. Lower doses of alcohol increase total sleep time whereas higher doses can lead to an acute withdrawal state that may result in sleep disruption in the latter half of the night.

The impact of alcohol on sleep latency (time to fall asleep) can be both, stimulating and sedative, dependent upon the dosage of alcohol and length of time between consuming alcohol and attempting to sleep. At low doses in the first hour after consumption as blood alcohol levels rise, the effect of alcohol is to stimulate sleep latency. The sedative effects are present at higher doses as blood alcohol levels decline.

The majority of studies have focused upon the sedative effects of alcohol, the few that have considered alcohol as a sleep stimulant suggest that late afternoon (Happy Hour) drinking 6 hrs before bedtime can disrupt sleep, even though alcohol is no longer in the brain when attempting to sleep (Landholt *et al.,* 1996).

In summary alcohol initially taken at bedtime has a paradoxical stimulating effect. It is however a sedative and not surprisingly the initial effect is to decrease the time required to get to sleep. However alcohol is more likely to lead to sleep disturbance particularly in latter part of the sleep period. During the latter sleep period a person who has drank alcohol may sleep in a fitful manner, awakening from dreams and finding it difficult to return to sleep (Foster, 2008).

For moderate consumption the sedating effects of alcohol are inconsistent. Moderate consumption is in the range of 0.4-0.8 g/kg (2-3 drinks)- 12 oz of beer, 5 oz wine, and 1.5 oz distilled spirits. Each drink equates to approx 5 oz of alcohol and lasts for several hours (Roehrs *et al.,* 1994). Up to six drinks sleep latency gradually decreases and the previously described rebound effect and increased arousal usually occurs at 2-3 hrs as blood alcohol concentration falls to zero. This is associated with increased levels of catecholamine later in the night. Assuming one glass of wine is metabolised at one unit per hour. If 5 glasses are consumed at 10 pm the blood alcohol levels will be approaching zero at 3 am which is the time when the rebound and arousal effects are heightened. In normal individuals (i.e. not alcohol dependent) tolerance to these changes in sleep architecture occur within 3-9 nights of moderate alcohol use. Tolerance to the sedative effects of alcohol is present after 3-7 days (Dufour *et al.,* 1992). There is a large body of literature concerning the links between sleep, alcohol and alcohol dependency (see Foster, 2008) in comparison little is known concerning the long-term impact of moderate amounts of alcohol in healthy individuals (Stein and Friedmann, 2005).

23.3.1 Alcohol and insomnia

Chronic insomnia is usually defined as difficulty initiating or maintaining sleep for a period longer than three weeks (Kupfer, 1997). Sleep disturbances that last less than three weeks are generally attributable to stress or acute illness. The definition of insomnia is one or more of the following that persists for at least one month (American Psychiatric Association, 2000):
* difficulty initiating sleep;
* difficulty maintaining sleep;
* waking up too early; and/or,
* sleep that is chronically non-restorative or of poor quality; in addition,
* day time impairment or distress related to night time sleep.

Impairments associated with insomnia (Edinger *et al.,* 2004) are:
* problems with fatigue;
* memory impairment;
* mood disturbances;
* proneness to errors;

- tension headaches;
- gastro-intestinal symptoms;
- sleep loss.

A general population study from 10 countries (n=35,327) using the Athens insomnia scale found a global insomnia rate of 32% (Soldatos *et al.,* 2005). The elderly and women are particularly vulnerable to insomnia and it has also been associated with lower education (Gellis *et al.,* 2005) unemployment and social deprivation (Paine *et al.,* 2004). General population studies also confirm a relationship between poor physical health and cigarette smoking, alcohol and insomnia (Peters *et al.,* 2011), approx 10-15% of individuals with chronic insomnia have underlying substance use problems (Dufour *et al.,* 1992).

Alcohol is known to have sedative properties and it is commonly used to self-treat insomnia as it is rare for an individual to seek professional help for insomnia (Ancoli-Israel and Roth, 1999). The same authors discovered that 15-28% of their participants have used alcohol to help them sleep. Johnson *et al.* (1998) found two thirds of their sample used alcohol in this way for less than a week but a minority (15%) had alcohol as a sleep aid for more than 4 weeks. Furthermore men were 1.37 times more likely to use alcohol to help them sleep. There is a paradox here, whilst 67% of those participants surveyed said that alcohol had helped them sleep there was a greater likelihood of daytime sleepiness (Costa *et al.,* 1996). This leads to the conclusion that with continued use alcohol loses its sedative/hypnotic properties quickly and often disturbed sleep results.

Approximately 30% of individuals from the general population use either alcohol, OTC or prescription drugs to cope with insomnia. Roehrs *et al.* (2002) in a US study have made comparisons of the characteristics of individuals who used alcohol compared to prescription drugs to cope with insomnia. Males were more likely to use alcohol and females OTC and prescription medication. Alcohol use was also associated with being single and day-time sleepiness. Prescription drug users were older, more likely to report sleepiness and be the most severely disadvantaged in terms of insomnia, neuroticism and day time fatigue.

A Swedish general population study provides some valuable insights into the role alcohol plays in insomnia (Ohayon and Bader, 2010). This was a randomly selected sample (n=1,209) (75% response rate) of adults aged 19-75. There was virtually the same number of male and female respondees. The main outcomes were three sleep states:
1. Difficulty falling asleep at least 4 days a week.
2. Difficulty falling asleep at least 4 days per week and two other criteria. Firstly awaking three times during the same night and secondly having difficulty getting back to sleep once having awakened.
3. NRS – this was deemed to be present if an individual felt tired upon awakening even if they had sufficient sleep (with reference to general population norms/or fell asleep without difficulty for 4 days per week or more). Therefore NRS was related to sleep quality.

Alcohol use was assessed by asking the participants if they 'never' used alcohol or did so 'sometimes' or 'daily'. Daily use was strongly related to NRS (i.e. sleep quality) following a regression analyses. The significant variables associated with NRS were as follows: being a woman, aged less than 65, divorced, living in an urban area, and drinking alcohol daily (odds ratio=4.6). Staying at home offered protection against NRS. There were a number of variables that lost significance once gender and aged were controlled for, these were having children under 6 years of age, being easily irritated, depressive mood, extroverted personality and anxious mood. The importance of this study is that it points to continued use of alcohol (even at low levels consumption levels were not assessed) impacting upon quality of sleep and that this is one of the few epidemiological studies that has attempted to tease out the impact of alcohol in 'normal' individuals. As will shortly be discussed the tendency to combine alcohol alongside a number of other variables is what characterises many epidemiological studies and limits many of the conclusions that can currently be drawn from the evidence base.

The importance of the Ohayon and Bader (2010) study is that it attempted to tease out the impact of alcohol on insomnia rather than a number of studies that have considered alcohol in combination with other factors. Arguably the best example is the Penn State Cohort (Vgontzas *et al.,* 2010) which is a general population study and found that insomnia was associated with diabetes or hypertension after controlling for age, race, education, body mass index, smoking, alcohol, depression, sleep disordered breathing and sampling weight. Alcohol use was defined as two or more drinks per day (USA). There have been a number of studies that have examined some conditions associated with sleep disturbance after controlling for demographic factors, body mass index, smoking and alcohol consumption. These include hypertension, coronary heart disease, type-2 diabetes and dysglycemia. Two international general population studies provide informative data concerning the relationship between alcohol and insomnia. A questionnaire based study conducted in Hong Kong (n=5,000) (Wong and Fielding, 2011) found that women were more likely to report sleep disturbance and poorer sleep quality. The following variables for the whole sample were associated with poor sleep scores (Pittsburgh sleep quality index) after step-wise regression analyses: non-full-time employment, existing long-term health problems, alcohol consumption four to seven occasions per week, higher anxiety depression scores, poor mental health and low self-perceived health status as measured by the short-form-12. Alcohol consumption was measured as follows: never/one to three times per month/one to two times per week/three or five times per week/daily or almost daily. A French WHO study (n=36,000) with a sample evenly matched for gender was conducted from 1999-2003, '*Sante mentale en population generale*' (Vaiva *et al.,* 2008). It examined general population variables that predicted suicide. The most comprehensive analysis (Danel *et al.,* 2010) was conducted in the Nord Pas De Calais region. The classical risk factors of gender (suicide was associated with post traumatic stress disorder and this was more prevalent for women), marital occupation and educational status and income were confirmed. A further logistic regression confirmed a number of mental illnesses that were high risk factors for suicide. They were (in order of greatest risk) depression, anxiety, psychotic disorders, alcohol abuse, drugs and insomnia. The link between alcohol and mood disorders notably anxiety and depression has been well documented (Kushner *et al.,* 2000).

Work in primary care (Vinson *et al.,* 2010) (n=1,699, 67% women, mean age 50.4 years, SD = 17.4) has shown that sleep disturbance related to hazardous or moderate drinking as assessed by AUDIT-C (short-form) scores and DSM-IV (diagnostic statistical manual) criteria for alcohol use disorders were associated with few sleep problems. Using alcohol to aid sleep was strongly associated with hazardous drinking. The odds ratio was 4.58 (2.97-7.08 95% confidence intervals) when this was compared with moderate drinking.

There is a study (Cheek *et al.,* 2004) that provides insight into insomnia, alcohol and middle-aged women (n=126, age range 40-55) compared to healthy sleepers. Sleep was assessed by diary entries for 6 days and home PSG monitoring. Women who had insomnia reported more variation in their sleep quality, in particular length of time to fall asleep. Regression analysis was able to assess the impact of what were termed 'life-style' variables. These were the following in combination; alcohol, caffeine, exercise, smoking and history of physical diseases and they explained 9-19% of the variance in relation to subjective sleep or objective PSG measures. These findings suggest that lifestyle practices, including moderate consumption of alcohol have a role to play in assessing sleep quality or insomnia but it is not a dominant one.

23.3.2 Alcohol and obstructive sleep apnoea

OSA is characterised by the 'recurrent partial or complete obstructions (hypopnoea/apnoeas) of the upper airway during sleep (American Academy of Sleep Medicine, 1999). For a diagnosis of OSA to be applied these obstructions must occur at least five times per hour, last 10 seconds and be accompanied by excessive daytime sleepiness and/or unrefreshing sleep and impaired daytime functioning (Berg, 2008). The apnoea-hypopnea index (Epstein *et al.,* 2009) is used to differentiate levels of OSA and these are shown in Table 23.1. Approx 2-4% Americans suffer from OSA (Strollo and Rogers, 1996).

If OSA is untreated there are implications in terms of morbidity and mortality, quality of life and working capacity (Laitinen *et al.,* 2003). It has been linked to cardiac arrests and accidents caused by tiredness (notably road accidents), asthma and diabetes (Philipson, 1993).

Table 23.1. Cut-off points for differing forms of obstructive sleep apnoea (OSA) using the apnoea-hypopnea index (AHI) (Epstein *et al.,* 2009).

AHI	Level of OSA
0-5	no diagnosis of OSA
5-15	mild (marked by chronic snoring)
16-30	moderate
Above 30	severe (disorder of the pharynx) - individual can wake up to 100 times per night

The Finnish guidelines for the prevention and treatment of OSA point out that the following are implicated in its development, smoking, being male and middle-aged or a post-menopausal women, obesity and alcohol (Laitinen *et al.,* 2003). The same authors state that general population interventions should focus upon reducing weight, alcohol and cigarette consumption.

Alcohol is linked to OSA because it relaxes upper airway dilator muscles and thus increases 'nasal and pharyngeal resistance' (Dawson *et al.,* 1993; Robinson *et al.,* 1985). This means that the time required for awakening following an episode of apnoea is prolonged (Krol *et al.,* 1984). Furthermore alcohol 'selectively depresses the hypoglossal nerve activity and alters carotid body chemoreceptor function' (Stein and Friedmann, 2005).

23.3.3 Alcohol and sleep deprivation and driving performance

The combination of alcohol and OSA has a cumulative impact on driving performance. Research has shown that those who have OSA and who consume 14 or more drinks per week (USA) were five times more likely to have a sleep-related accident compared to lower levels of consumption (Aldritch *et al.,* 1993). The impairment caused by OSA and alcohol consumption at levels where it is still legal to drive is akin to sleep deprivation rather than a diminution in cognitive or performance/motor skills (Hack *et al.,* 2001).

There is a body of work that has examined driving performance, sleep deprivation and alcohol in individuals without OSA. Powell *et al.* (2001) has shown that driving performance levels in a group of healthy sleep-deprived adults (defined as one night without sleep- (acute) or 2 hrs or less sleep for seven days- (chronic)) compared to a group who were given alcohol at a blood alcohol concentration of 0.089 g/dl were comparable. The blood alcohol concentrations were at the level where it is illegal to drive and the authors concluded that driving performance whilst sleep deprived had the same impact on driving risks as driving illegally whilst under the influence of alcohol. The combination of alcohol at a level below the legally endorsed limit for driving (USA) (0.035 g/dl) and partial sleep deprivation also has a significant impact upon driving performance and awareness of the risk of crashing (Banks *et al.,* 2004). Furthermore there appear to be important gender differences. A group of 20 healthy volunteers (23 years mean) (9 men, 11 women) were subdivided into two groups (PSD vs. PSD+A) and compared. PSD was defined as being restricted to 5 hrs sleep the night(s) before testing. Those participants in the PSD + A had more 'micro-sleeps', impaired driving simulator performance, and a poorer perception of the likelihood of crash risk. Women who were only partially sleep deprived had a greater perception of crash risk and awareness of their own limitations than men, but in the PSD + A group these differences disappeared. Todd Arnedt *et al.* (2001) found that 'increased wakefulness' and increasing blood alcohol levels resulted in a dose-related diminution in driving performance, in particular with regard to assessment of risk. Further work in the UK (Barrett *et al.,* 2005) indicates there is no safe blood alcohol level when a driver is 'sleepy.' Eight healthy young men who were given alcohol at level that ranged from 40-28 mg alcohol/100 ml of blood which is well below the UK legally endorsed 'safe' alcohol limit for driving, had their driving performance assessed. Each was asked to drive in a simulator on a 'monotonous highway' for

2 hrs from 18:00 and the following were assessed: driving impairment, subjective sleepiness and electroencephalogram sleep measures. Sleep restriction resulted in poor driving performance and sleepiness. Alcohol alone did not impair either of the two previously mentioned variables. However the combination of sleep restriction and alcohol resulted in the poorest performance in all three measurements.

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Summary points

- Vitamin D is an essential nutritional element, the role of which is not yet completely understood.
- The diseases known to be associated with vitamin D deficiency (VDd) create symptoms which are likely to interfere with sleep quality and quantity, and are likely to cause daytime neurocognitive impairment symptoms overlapping with those caused by sleep deprivation and other sleep disorders.
- VDd may enhance anatomic changes (tonsillar hypertrophy, upper airway hypotonia) predisposing to development of obstructive sleep apnea (OSA).
- VDd may independently modulate its presentation via enhancement of inflammatory constituents of Process S.
- Individuals presenting with sleep-wake complaints should be queried about risk factors for VDd, and should be supplemented appropriately if deficiency is documented.
- Further research is needed to fully evaluate the role that vitamin D plays in sleep, sleep disruption, excessive daytime sleepiness (EDS), and daytime neurocognitive impairment.

24. Vitamin D deficiency, sleep, sleep disruption, and daytime neurocognitive impairment

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Abstract

Vitamin D is a fat-soluble secosteroid that interacts with intranuclear vitamin D receptors (VDRs) to effect changes to DNA transcription. VDRs are located in numerous tissues of the body, including brain, components of the immune system, and skeletal muscle. Worldwide, vitamin D deficiency (VDd) is highly prevalent, with identified risk factors including dark skin pigmentation, obesity, advanced age, limited sun exposure, pregnancy, and chronic use of steroids or anticonvulsant medications. VDd causes diseases of bone demineralization known as rickets (demineralization at epiphyseal growth plates) and osteomalacia (demineralization at areas of increased bone turnover) and a painful myopathy of skeletal muscles (osteomalacic myopathy). Research on VDd and its interaction with sleep is scant, though circumstantial evidence suggests that a complex relationship is likely to exist. VDd-related pain likely promotes sleep disruption directly. VDd is associated with increases in the sleep-regulating substances TNF-α and IL-1, and possibly prostaglandin D2, suggesting that VDd may be a cofactor for the development of daytime neurocognitive impairment. VDd may also increase the risk for obstructive sleep apnea (OSA), via promotion of adenotonsillar hypertrophy, airway hypotonia, and chronic rhinitis. Further research is needed to establish the complex relationship between VDd, normal sleep, sleep disruption, and daytime neurocognitive impairment.

Keywords: vitamin D, sleep, sleepiness, obstructive sleep apnea, osteomalacia, rickets

Abbreviations

BMI	Body mass index
COX-2	Cyclooxygenase 2
EDS	Excessive daytime sleepiness
ESS	Epworth sleepiness scale
IH	Idiopathic central nervous system insomnia
IL	Interleukin
OSA	Obstructive sleep apnea
OSAS	Obstructive sleep apnea syndrome
PD2	Prostaglandin D2
PTH	Parathyroid hormone
SRS	Sleep regulatory substance
TNF-α	Tumor necrosis factor α
VDd	Vitamin D deficiency
VDR	Vitamin D receptor

24.1 Introduction

The last decade witnessed an intense surge of interest in vitamin D, fueled by an increasing awareness of the widespread distribution of VDR in various tissues of the body, including brain, various components of natural and specific immunity, myocardium, skeletal muscle, prostate, and breast. Published studies in the past several years have yielded compelling data suggesting an inverse relationship between circulating 25-hydroxyvitamin D, natural sun exposure (or both) and risk for a diverse array of human diseases, including schizophrenia, multiple sclerosis, cardiovascular disease, and various cancers. VDd has been shown to be associated with increased risk for falls, depression, heart failure, progression of chronic obstructive pulmonary disease, and risk for childhood asthma (Holick, 2007).

It is therefore somewhat surprising that vitamin D remains essentially unexplored as a sleep medicine issue. The purpose of this chapter is to examine the existing scientific evidence that vitamin D may be related to normal sleep, sleep disorders, and daytime neurocognitive impairment, particularly EDS. To do this, we must first review the basic biochemistry of vitamin D to provide a framework for the diseases well-appreciated to result from its deficiency. Following that will be a basic review of sleep, sleepiness, and sleep disorders. This will allow an understanding of how, potentially, VDd may participate in the creation or modification of pathologies of sleep and daytime neurocognitive impairment. Suggested questions for further research will then be listed, followed last by some concluding remarks.

24.2 Basic physiology of vitamin D

'Vitamin D' refers to a collection of fat-soluble secosteroids available from select dietary sources (Table 24.1) or manufactured in the human body in a multi-step process involving multiple compounds (Table 24.2).

Upon exposure to specific wavelengths of ultraviolet light (290-315 nm), 7-dehydrocholesterol transforms to vitamin D3 (cholecalciferol), the form of vitamin D which is found in animal products and a few commercially available supplements. Vitamin D2 (ergocalciferol) is a plant-derived product, formed when ergosterol is exposed to light. Most commercially available supplements contain this form.

In order to become biologically active, vitamin D (either D3 or D2) must undergo two hydroxylation reactions. First, it is transported in the bloodstream, bound to vitamin D binding proteins. In the liver, it is hydroxylated to form 25-hydroxyvitamin D (calcidiol), the 'storage' form of the vitamin. This compound reflects overall vitamin D supply from both dietary and light-induced manufacturing sources, and is typically measured by clinicians to determine vitamin D status. The second hydroxylation step occurs in the kidneys, enzymatically controlled by 25-hydroxyvitamin D-1α-hyroxylase, producing the biologically active form of the vitamin 1,25 dihydroxyvitamin D (calcitriol), regulated via a complex series of feedback loops by PTH, serum calcium and phosphorus levels, and by calcitriol itself.

The structure of vitamin D is similar to that of steroid hormones, being 'built' as it is from the same cholesterol carbon skeleton as more 'familiar' steroid hormones, such as cortisol (Table 24.2).
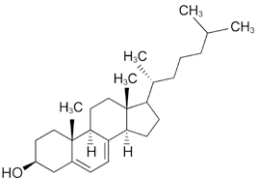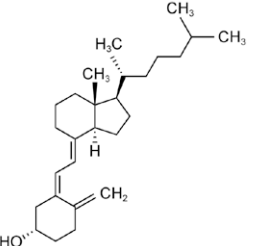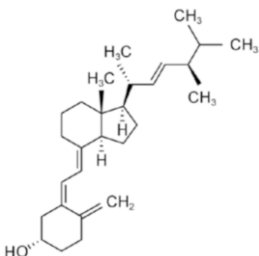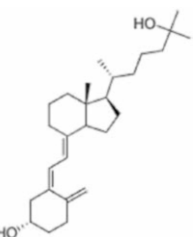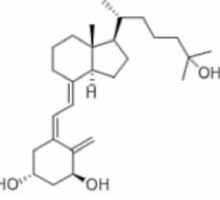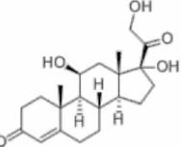
Table 24.1. Dietary sources of vitamin D (adapted from Holick, 2007).

Source	Form of vitamin D	Approximate content
Sun dried shiitake mushrooms, 100g	Vitamin D2	1,600 IU
Cod liver oil, 5 cc	Vitamin D3	400-1000 IU
Wild-caught salmon, 100 g	Vitamin D3	800 IU
Canned salmon, 100 g	Vitamin D3	500 IU
Canned sardines, 100 g	Vitamin D3	300 IU
Canned mackerel, 100 g	Vitamin D3	250 IU
Farmed salmon, 100 g	Vitamin D3 or D2	200 IU
Fortified milk, 250 cc	Vitamin D3	100 IU
Fortified breakfast cereal, 1 serving	Vitamin D3	100 IU
Fresh shiitake mushrooms, 100 g	Vitamin D2	100 IU
Egg yolk	Vitamin D3 or D2	20 IU

IU = international unit.

Table 24.2. Forms of vitamin D and related compounds.

Form	Chemical structure
7-dehydrocholesterol	
cholecalciferol	
ergocalciferol	
calcidiol	
calcitriol	
cortisol	

Not surprisingly, it performs its biological functions in a 'hormone-like' way – in the nuclei of cells, effecting changes in DNA transcription. Calcitriol interacts with intranuclear VDRs and retinoid-X receptors, forming heterodimers that subsequently bind to specific regions of DNA and behave as transcription factors.

Some of the earliest understood functions of calcitriol include its actions on the gut and bone, which help maintain calcium and phosphate equilibrium. In the gut, calcitriol effects an increase in calcium absorption from the diet, by working to increase epithelial calcium channels and calcium binding proteins (calbindin 9K). In the bone, calcitriol induces the maturation of osteoclasts, which mobilize calcium and phosphorus from the bone. In the kidneys, it promotes calcium reuptake.

24.3 Diseases caused by vitamin D deficiency

In VDd, the body compensates by increasing production of PTH, promoting increased activity of renal 25-hydroxyvitamin D-1α hydroxylase, the enzyme responsible for increasing production of calcitriol. If this condition becomes chronic, the parathyroid glands may become constitutively overactive, with a resulting secondary hyperparathyroidism. As the condition continues, the calcium phosphate matrix of bone is increasingly tapped, and the bones become progressively demineralized. At some point, it is difficult for the body to maintain normal serum concentrations of calcium and phosphate, and the deficiency state becomes clinically more apparent.

The calcidiol level necessary to maintain optimum health is the subject of considerable debate. In general, PTH levels are inversely related to calcidiol (25-hydroxyvitamin D) at calcidiol levels of <75 nmol/l (Figure 24.1) (Chapuy *et al.*, 1997). For calcidiol levels >100 nmol/l, the PTH value reaches a nadir and remains flat. Intestinal calcium absorption is impaired at a level of 50 nmol/l, with a dramatic improvement in calcium absorption seen at a level of 75 nmol/l. For these reasons, most authorities set the benchmark for 'deficiency' at calcidiol levels <50 nmol/l and 'insufficiency' at <75 nmol/l (Holick, 2007). PTH levels remain normal in black individuals at lower values of calcidiol compared with Caucasians, suggesting that the definition of 'deficiency' may require adjusting for race (Wright *et al.*, 2012).

VDd has been described as a 'global pandemic'. The prevalence estimations depend heavily on the population under study, with risk factors including obesity, limited sun exposure, dark skin pigmentation, pregnancy, poverty, malabsorption syndromes (including prior gastrectomy, bariatric surgeries, and coeliac disease), chronic steroid use, chronic anticonvulsant use, and advancing age. There are several diseases known to be caused by VDd, which will be briefly reviewed in Table 24.3.
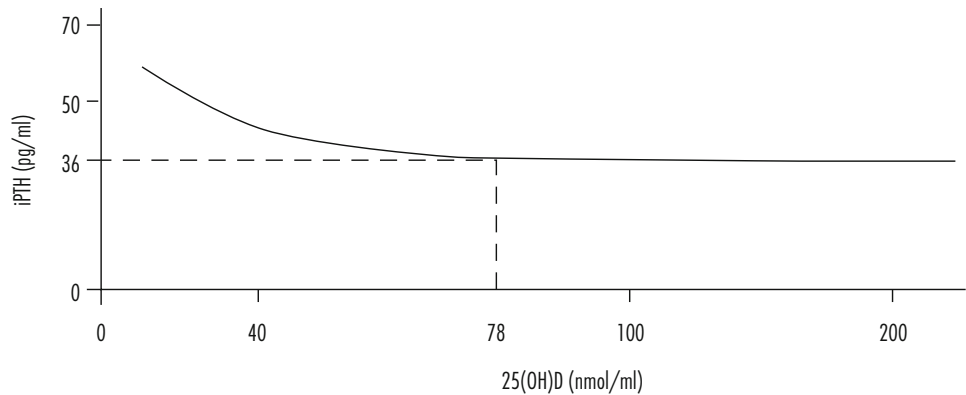
Figure 24.1. Relationship between intact parathyroid hormone (iPTH) and calcidiol (25 (OH) D) values in a population of urban dwelling adults (n=1,569). The iPTH plateau occurs at a calcidiol concentration higher than 78 nmol/l. When values are lower than 78 nmol/l, serum iPTH values begin to increase (Chapuy *et al.,* 1997).

Table 24.3. Diseases known to be associated with vitamin D deficiency.

Disease name	Pathophysiology	Clinical features	Notes
Rickets	inadequate bone mineralization at cartilage of ephiphyseal growth plates	bony pain, delayed closure of the frontal fontanelle, progressive bowing of the legs, enlargement of the costochondral junction	syndrome can also be caused by severe calcium- or phosphate deficient diets, malabsorption syndromes (e.g. celiac sprue), and renal phosphate wasting (e.g. Fanconi Syndrome)
Osteomalacia	inadequate bone mineralization at sites of newly formed osteoid in areas of bone turnover	bony pain & tenderness, muscle weakness, difficulty walking/ waddling gait; often associated with secondary hyperparathyroidism	syndrome can also be caused by renal phosphate wasting; correct diagnosis of osteomalacia is often delayed due to nonspecific symptoms
Osteomalacic myopathy	may involve defective cellular transport in skeletal muscle; hypocalcemia/hypophosphatemia may play a role	muscle pain, proximal muscle weakness, muscle wasting, difficulty walking	cofactor for development of statin-induced and aromatase-inhibitor- associated myopathy

24.3.1 Rickets

Rickets is the prototypical syndrome of childhood VDd. The classic skeletal malformations are caused by defective mineralization of the epiphyseal growth plates, and have readily-identifiable features. The 'rachitic rosary' is a description of the bulging appearance of the anterolateral costochondral junctions, draping across the thorax in a pattern similar to a necklace. The softened long bones bend with time and weight-bearing to form bowed legs in various patterns. Myopathic symptoms of weakness, diffuse pain, and general debility are common. An increase in generalized sweating, attributed to bone pain, is also noted. Individuals with rickets are understood to have an increased propensity for infectious diseases, possibly due to immune system dysregulation.

24.3.2 Osteomalacia

When bone mineralization is compromised in areas of bone turnover besides the growth plates, the term 'osteomalacia' is used. In children, osteomalacia may coexist with rickets. Adults with VDd have mineralization defects that occur exclusively in areas of bony turnover because the epiphyseal plates have closed. As with rickets, osteomalacia is associated with diffuse bone pain, likely related to increasing water content in the demineralized bone, leading to swelling, stretching the sensitive periostium (Holick, 2007). Typically, this symptom can be elicited by demonstrating marked tenderness of the tibial plateau.

24.3.3 Hypovitaminosis D myopathy

VDd can be accompanied by a painful myopathy syndrome (termed 'osteomalacic myopathy' or 'hypovitaminosis D myopathy'), with resultant proximal muscle weakness, diffuse muscle pain, and increased likelihood for falls and injury (Russell, 1994). VDd was recently identified as a cofactor for the development of statin-induced myopathic pain (Ahmed *et al.*, 2009). Many individuals who developed statin-induced myalgias experienced resolution of the syndrome upon identification and remediation of VDd. VDd is also a cofactor for aromatase-inhibitor associated myalgias, with supplementation shown to improve tolerability of these agents (Rastelli *et al.*, 2011). VDd is frequently found among patients presenting with chronic nonspecific musculoskeletal pain, patients often diagnosed as suffering from fibromyalgia or degenerative joint disease (Plotnikoff and Quigley, 2003). Furthermore, osteomalacic myopathy can occur in the absence of any elevation in serum alkaline phosphatase, the most widely-used indicator of osteomalacic bone turnover (Glerup *et al.*, 2000).

24.3.4 Secondary hyperparathyroidism

As mentioned earlier, secondary hyperparathyroidism often accompanies chronic VDd, the unregulated parathyroids mobilizing bony calcium to the point that hypercalcemia ensues. A complete review of the disease accompanying the hyperparathyroid state is beyond the scope of this chapter, but a classic medical-student mnemonic recalls the systemic nature of the disease: 'Stones, bones, groans, and moans.' Nephrolithiasis and nephrocalcinosis ('stones'), osteomalacia

and pathologic fractures ('bones'), abdominal complaints such as constipation, indigestion, and nausea ('groans'), and central nervous system complaints such as depression, lethargy, fatigue, and memory loss ('moans') are the key features of the disorder.

24.4 The biological regulation of sleep

'Sleeping' is a seemingly simple act that – when manifested in health – simply 'happens' with no requirement for effort on the part of the sleeper. In truth, the activity we universally accept as 'sleep' and the symptom we understand as 'sleepiness' result from a complex interplay of neurotransmission, metabolism, temperature, immunology, and psychology, the detailed discussion of which would fill an entire textbook and will not be attempted here. However, in order to introduce mechanisms by which VDd may contribute to sleep-related complaints, a basic discussion of some of the mechanisms of sleep is required.

The fundamental mechanism for sleep/wake regulation is best explained with the description of two independent systems (Figure 24.2) (Borbely, 1982). The first – termed 'Process S'– is best understood as a wake-driven homeostatic sleep 'pressure' which builds while the individual is awake and diminishes during sleep. There are many biological substrates mediating Process S – termed 'sleep regulatory substances' – the best-studied of which are adenosine, PD2, IL-1, and TNF-α (Opp, 2005).

While process S can be best conceived of as a 'use-dependent' phenomenon (i.e. the more time spent awake, the greater the sleep propensity), process C ('C' for 'circadian') is a phenomenon independent of prior wakefulness. Process C is driven instead by the suprachiasmatic nuclei, a
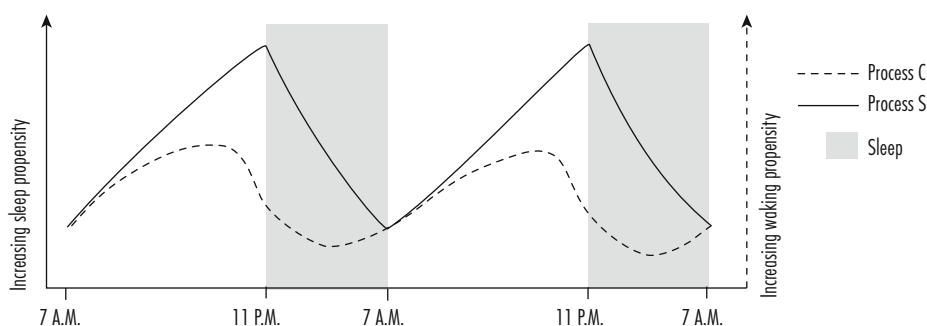
Figure 24.2. Process S and process C. Sleep propensity can be explained with a dual-process model. 'Process S' (solid line) builds during wakefulness in a use-dependent fashion ('sleep pressure'), and dissipates during sleep. The left sided y-axis shows that if process S increases, increased sleep propensity is seen. Process C is 'clock-driven,' and functions to stabilize wakefulness despite mounting homeostatic sleep pressure. Process C is most active during the second half of the waking day, and relatively quiescent during sleep. The right-sided y-axis shows that if process C increases, increased waking propensity is seen.

biological clock that achieves synchrony with the day/night variation of earth primarily via photic signaling from the retina to the hypothalamus. Process C is effected primarily via the activity of wake-promoting and wake-stabilizing neurotransmitters of the ascending reticular activating system (including hypocretin, acetylcholine, dopamine, norepinephrine, and histamine), with additional modulation from melatonin, which in humans has mild hypnotic (sleep-inducing) effects and also exerts circadian phase-dependent effects on the timing of the circadian rhythm itself.

24.4.1 Sleepiness, excessive daytime sleepiness, and daytime neurocognitive impairment

The feeling commonly described as 'sleepiness' can be functionally defined as 'having an increased propensity to fall asleep.' Though sleepiness can be a comforting feeling when it is physiologically normal (i.e. at the end of a long working day), it can be an unwelcome or even disabling symptom when it is chronic or unrelieved by the act of sleeping itself.

By far, the most common etiology for EDS is insufficient sleep, but some persons experience chronic EDS despite what would be considered adequate time spent asleep at night. A complete sleep-related history, physical exam, and polysomnography in such settings may reveal evidence for chronic sleep disruption due to specific diseases, such as OSA, restless leg syndrome or a sleep-related movement disorder such as periodic limb movements of sleep. Other individuals suffer from EDS caused by dysfunction of sleep regulation, conditions termed 'primary hypersomnia' syndromes, examples of which are narcolepsy and IH.

The term 'neurocognitive impairment' is often used to describe the myriad symptoms aside from EDS which can result from inadequate sleep. Somatic symptoms such as headaches, irritable bowel complaints, and muscle pain are all commonly associated with sleep deprivation. Mood disturbances such as anxiety or depression are also commonly reported. Sleep deprivation-induced deficits in alertness and concentration may result in an inappropriate diagnosis of attention deficit disorder (McCarty, 2010a). The nonspecificity of these symptoms represents a unique challenge to the practicing sleep medicine specialist, in that any identifiable source of sleep disruption and/or daytime neurocognitive impairment should be sought and, if possible, specifically remedied. A methodical approach to complaints of subjective sleep disturbance or daytime neurocognitive impairment may reveal more than one etiology for such symptoms, potentially increasing the likelihood of successful intervention and improved outcomes (McCarty, 2010b).

24.5 Potential mechanisms by which vitamin D deficiency may contribute to sleep/wake complaints

Though VDd has potential to interact with sleep/wake-related complaints in a number of different ways, published research on this issue is limited. Nonetheless, there are data to support a causal link between VDd and conditions generally accepted to contribute to sleep/wake complaints (Figure 24.3).

24.5.1 Vitamin D deficiency, pain, and sleep

Individuals with chronic pain have poorer quality sleep and shorter sleep duration compared with individuals who report no such symptoms (Okura *et al.*, 2008). Moreover, individuals with decreased total sleep time report a higher degree of spontaneous daytime somatic pain symptoms, and are likely to report pain with a lesser degree of stimulation, compared with individuals who are not sleep-deprived (Edwards *et al.*, 2008). Sleep deprivation-associated increases in pain perception are likely to be mediated by increases in IL-6 (Haack *et al.*, 2007). Chronic pain also negatively impacts an individual's mood and outlook, which may further increase the subjective experience of daytime impairment, in the form of fatigue, despair, or depression (Nicassio *et al.*, 2002).
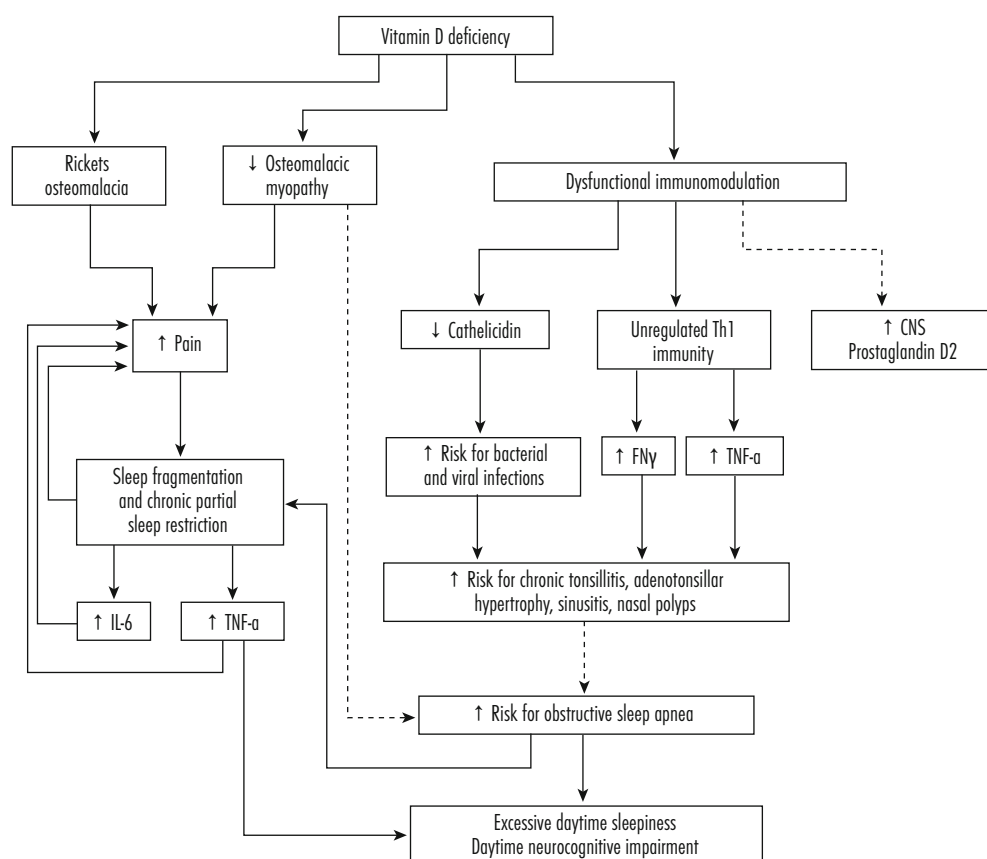
Figure 24.3. Mechanisms by which Vitamin D deficiency may interact with sleep/wake complaints. A dotted line indicates that the relationship is hypothesized, but not yet proven.

IL = interleukin; TNF-a = tumor necrosis factor a; FN = fibronectins; Th = T-cells helper

Many researchers have found that populations with nonspecific musculoskeletal pain have a high prevalence of undiagnosed VDd, suggesting that the presence of chronic nonspecific musculoskeletal pain should prompt careful consideration of possible deficiency (Holick, 2003). Similarly, among ambulatory sleep medicine specialty clinic patients endorsing chronic moderate-to-severe pain interfering with sleep or impacting daily activity, VDd (calcidiol <50 nmol/l) was found in over half (McCarty and Reddy, 2011).

A causal association between VDd and musculoskeletal pain is well-established, though many unanswered questions still exist. Some patients with documented severe VDd experience few somatic symptoms, while others may have pain that does not improve following appropriate supplementation of vitamin D, suggesting that the symptom was unrelated to the deficiency in the first place. Distinguishing *a priori* which patients will respond to supplementation is difficult.

24.5.2 Is there a link between vitamin D deficiency and obstructive sleep apnea syndrome?

OSA is term describing polysomnographic evidence of periodic obstruction of the upper airway during sleep, leading to intermittent hypoxia and/or hypercarbia affecting 2-4% of the adult population (Young *et al.*, 1993). The diagnosis of OSAS requires OSA to be associated with subjective sleep complaints or daytime neurocognitive impairment. Risk factors for the development of OSAS include obesity, large neck circumference, adenotonsillar hypertrophy, retropositioning of the mandible, low-lying or redundant soft palate, chronic nasal airflow limitation, and race – with Blacks, Hispanics, and Native Americans being higher risk, compared to Caucasians.

Daytime impairment symptoms in individuals with OSAS likely result from chronic partial sleep deprivation (frequent awakenings, difficulty returning to sleep due to sympathetic hyperstimulation) combined with the pro-inflammatory effects of intermittent hypoxia, which results in further elaboration of SRSs, particularly TNF-α and PD2 (Ryan *et al.*, 2008). However, polysomnographically-confirmed OSA has been described in individuals who fail to manifest any evidence of cardiovascular disease or daytime impairment (Pavlova *et al.*, 2008), underscoring the notion that there is variation in individual resilience against the physiologic stress of OSA, and suggesting that other elements (genetic, environmental, etc.) probably act as cofactors for the illness that results from it.

There are no published data directly addressing a possible relationship between VDd and OSAS. However, circumstantial evidence hints that such a relationship may exist, including anatomic changes to the upper airway which may result from VDd and the clustering of OSAS and VDd in similar at-risk populations. Furthermore, VDd may influence the presentation of OSA (or, for that matter, other sleep-disrupting forces) by directly stimulating the elaboration of cytokines promoting daytime neurocognitive impairment, particularly the SRSs TNF-α and PD2.

The fact that vitamin D deficiency contributes to hypotonia and myopathy of skeletal muscle is well-established (Russell, 1994). Heritable myopathies (e.g. Duchenne muscular dystrophy,

myotonic dystrophy) are known to place individuals at risk for OSAS. OSA following statin-induced myopathy (Ebben *et al.*, 2008) and steroid-induced myopathy (Yigla *et al.*, 2003) have been described. It is reasonable to speculate that VDd may elevate an individual's risk in a similar fashion, due to upper airway hypotonia combined with weakness of ventilatory skeletal muscles.

Upper airway crowding in OSAS is caused by anatomic factors besides pharyngeal hypotonia. One of the most important of these, particularly in children, is hypertrophy of the tonsils and adenoids. Evidence exists to support the idea that VDd predisposes to tonsillar enlargement. T-cell populations derived from human tonsils display decreased mitogen-induced proliferation in the presence of calcitriol, suggesting that vitamin D may offer protection from development of problematic tonsillar hypertrophy (Nunn *et al.*, 1986). If VDd contributes causally to tonsillar hypertrophy, it may also do so indirectly, via its immunologic impact on susceptibility to viral infection (Grant, 2009). Recent work complements these findings, noting low calcidiol levels in individuals who had undergone tonsillectomy for various reasons; those individuals with the greatest degrees of tonsillomegaly were most likely to have VDd (Reid *et al.*, 2011). Taken together, these data imply that VDd predisposes to adenotonsillar hypertrophy, and suggests that early identification and treatment may be of value.

The nasal airway is also an important source of upper airway resistance, and sources promoting chronic rhinitis and nasal polyposis would be expected to increase the risk for OSA. In children, chronic nasal airflow limitation can lead to obligate mouth-breathing, which can negatively impact facial skeletal development, leading to high-arched palate, bilateral maxillary posterior cross-bite and class II malocclusion, skeletal abnormalities that predispose to development of OSA.

Recent work is starting to illustrate how VDd impacts the nasal airway. There has been considerable interest recently on the impact of vitamin D on cellular and natural immunity. Vitamin D deficiency leads to altered immunomodulation, favoring unregulated Th-1 over Th-2 immunity (Kamen and Tangpricha, 2010). This results in an antigenically-stimulated upregulation in multiple pro-inflammatory cytokines (TNF-α among them), providing an explanation for the development of chronic rhinosinusitis (Abuzeid *et al.*, 2012). Epidemiologic and laboratory data are supportive of this: low calcidiol levels have been documented in urban-dwelling black children with chronic rhinosinusitis (Pinto *et al.*, 2008) and calcitriol was shown to inhibit nasal polyp fibroblast proliferation *in vitro* (Rostkowska-Nadolska *et al.*, 2009).

24.5.3 Can vitamin D deficiency independently lead to daytime neurocognitive impairment?

VDd may independently contribute to daytime neurocognitive impairment via dysfunctional immunomodulation. Recently reported was a case in which a young woman presented with symptoms highly suggestive of IH. Following identification and remediation of VDd, her EDS resolved (McCarty, 2010c). Objective measures of sleep did not explain the improvement in EDS symptoms, and it was postulated that the mechanism for improvement might involve changes in vitamin D-associated SRSs. This raises the interesting question of whether VDd could be an

independent cause of EDS, and/or behaves as a cofactor which increases the risk of developing symptoms in the setting of other sleep-disrupting forces, including OSA.

If VDd were indeed such a cofactor, one would expect (1) asymptomatic patients with OSA would have fewer risk factors for VDd compared with patients suffering from OSAS and (2) VDd and OSAS would be found in similar patients and would be associated with similar adverse health events. Though these issues have not been directly addressed in the scientific literature, circumstantial evidence implies that these relationships may exist.

The asymptomatic population studied by Pavlova *et al.* comprised physically-active adults of normal weight (BMI <30), a group with lower expected risk for VDd compared with groups considered to be high-risk for OSAS (obese patients, Blacks, Hispanics, Native Americans). Moreover, low socioeconomic status – itself a risk factor for development of VDd (Weng *et al.*, 2007) – was shown to be an unexpected risk factor for development of pediatric OSAS, even after controlling for BMI and race (Spilsbury *et al.*, 2006). In addition, mounting evidence suggests that VDd and OSAS are associated with common adverse cardiovascular outcomes. Like OSAS, VDd is linked to hypertensive disease, cardiovascular disease and the metabolic syndrome (Maki *et al.*, 2009).

If vitamin D is related to EDS, the relationship is likely to be complex. In patients with calcidiol ≥50 mmol/l, we found a statistically significant inverse trend between scores on the ESS and calcidiol levels (McCarty *et al.,* 2012). In patients with calcidiol <50 mmol/l (i.e. those with VDd), a significant *direct* relationship was seen in black patients (i.e. lower calcidiol leading to lower scores on the ESS), while a nonsignificant trend towards an inverse relationship was seen in white patients, suggesting that VDd likely provokes other changes to somehow counterbalance sleep-promoting factors in blacks, but not in whites. What these other factors might be is, at present, only the subject of speculation, but could include sympathetic stimulation due to pain or development of other disorders such as sleep apnea.

If VDd causes daytime neurocognitive impairment independently of other sleep disorders, it may do so via its effects on the immune system. The SRS TNF-α is a pro-inflammatory cytokine produced in humans mainly by macrophages, and is a part of the normal immune response to injury or infection. Sleep deprivation, acutely or chronically, can increase TNF-α levels in healthy subjects (Chennaoui *et al.*, 2011). Daytime neurocognitive impairment associated with chronic inflammatory conditions (e.g. multiple sclerosis, obstructive sleep apnea) may be mediated by TNF-α (Kos *et al.,* 2008). Moreover, many non-EDS symptoms commonly attributed to sleep loss (such as irritability, poor concentration, and enhanced sensitivity to pain) can be elicited simply by administration of TNF-α (Krueger *et al.*, 2011).

An inverse relationship between calcidiol levels and TNF-α has been shown to exist (Bellia *et al.*, 2011). In another study, two important SRSs (TNF-α and IL-1), were discovered to have an inverse relationship to circulating calcidiol levels (Khoo *et al.*, 2011). Furthermore, calcitriol was shown to inhibit macrophage production of TNF-α following stimulation by lipopolysaccharide, suggesting causality in the inverse relationship rather than mere association (Kuo *et al.*, 2010).

The SRS PD2 is derived from arachadonic acid, with the rate-limiting step being controlled by COX-2. It is proven to be a central regulator of sleep in animals and is likely to be one factor responsible for the symptoms of sleepiness in obstructive sleep apnea (Barcelo *et al.*, 2007). Vitamin D was shown to effectively down regulate the production of COX-2 in prostate tissue (Feldman *et al.*, 2007) suggesting that VDd could result in an increase in circulating PD2. At present, it is not known whether there is a correlation between vitamin D status and biologically-relevant circulating levels of PD2.

24.6 Research agenda

At present, much remains to be discovered about the role vitamin D may play in normal sleep, sleep disruption, and daytime impairment:

- Additional studies should be performed to determine if VDd directly causes daytime neurocognitive impairment. Because daytime neurocognitive impairment includes symptoms which are often vague or nonspecific, such research will require inquiry into physical symptomatology (such as nonspecific pain), quality of life, mood symptoms, and higher cognitive functioning.
- The role of VDd in the development of OSA and OSAS needs to be elucidated. Such studies should focus on the relationship between VDd and the development of predisposing obstructive upper airway anatomy, and in determining if vitamin D status helps explain the difference between asymptomatic OSA and OSAS.
- Whether VDd independently causes EDS needs to be investigated. Such studies would focus on the relationship between circulating calcidiol levels and subjectively reported sleepiness (such as the Epworth Sleepiness Scale score), objectively measured sleepiness (such as multiple sleep latency testing) and on SRSs, with particular attention to PD2 and TNF-α.
- The benefits of successful vitamin D replacement with respect to neurocognitive impairment symptoms, EDS and OSA severity needs to be evaluated.

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Summary points

- Head and neck cancers afflict a wide variety of patients worldwide. The treatments for these malignancies have improved over the past few decades and a significant portion of patients will experience long-term survival after diagnosis.
- Sleep problems are common and often severe in this group. Risk factors that predispose patients to head and neck cancer are also important co-factors in sleep disorders.
- Smoking, alcohol abuse, advanced age, hypothyroidism are among the risk factors that are common in both head and neck cancer patients and patients with sleep problems.
- In the past two decades researchers have identified very high prevalence of sleep problems, before and after treatments, in these patients. Sleep problems in form of obstructive sleep apnea and subjective sleep quality tend to correlate with xerostomia, depression, pain, presence of tracheostomy and feeding tubes among other factors.
- Diagnosis is based on subjective questionnaires and sleep studies. The prevalence can be as high as 90%.
- Treatments are available and effective. These include addressing pain and depression, correcting underlying hypothyroidism, alleviating xerostomia and removing unnecessary tracheostomies and feeding tubes.
- Treating obstructive sleep apnea is particularly difficult in this population and compliance can be quite low.
- Improving quality of sleep has shown to improve the overall quality of life and productivity of the survivorship group.
- Sleep problems are a fertile ground of research in head and neck oncology and more data is expected to be available on this topic in the coming years.

25. Oral cavity and oropharyngeal cancers and sleep

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Abstract

Head and neck cancers comprise 6% of cancer cases worldwide. Oral cavity and oropharynx cancers are among the most common head and neck cancers. The treatments for these malignancies have improved over the past few decades and a significant portion of patients will experience long-term survival after diagnosis. Sleep problems are common and often severe in this group. Risk factors that predispose patients to head and neck cancer are also important co-factors in sleep disorders. Smoking, alcohol abuse, advanced age, hypothyroidism are among the risk factors that are common in both head and neck cancer patients and patients with sleep problems. The available data on the prevalence, severity and impact of sleep problems in this group is extremely limited currently. In the past two decades researchers have identified very high prevalence of sleep problems, before and after treatments. Sleep problems in form of obstructive sleep apnea and subjective sleep quality tend to correlate with xerostomia, depression, pain, presence of tracheostomy and feeding tubes among other factors. Diagnosis is based on subjective questionnaires and sleep studies. Treatments are available and effective. These include addressing pain and depression, correcting underlying hypothyroidism, alleviating xerostomia, treating obstructive sleep apnea and removing unnecessary tracheostomies and feeding tubes. Improving quality of sleep has shown to improve the overall quality of life and productivity of the survivorship group. Sleep problems are a fertile ground of research in head and neck oncology and more data is expected to be available on this topic in the coming years. In this chapter the incidence, diagnosis and treatment of sleep problems in oral cavity and oropharynx cancer patients is discussed. The available data is reviewed and analyzed. An algorithm is proposed to approach and treat sleep problems in these patients.

Keywords: diagnosis, treatment, head and neck cancer, obstructive sleep apnea

Abbreviations

CPAP	Continuous positive airway pressure
EORTC	European organization for research and treatment of cancer
ESS	Epworth sleepiness scale
HPV	Human papilloma virus
MOS	Medical outcomes study
OSA	Obstructive sleep apnea
QLQ-C30	Quality of life questionaire-C30

25.1 Introduction

Head and neck cancers comprise around 6% of cancer cases worldwide (Jemal *et al.*, 2011). The five-year prevalence of oral cavity and oropharynx cancers is more than a million cases globally. While the incidence of oral cavity tumors is stable or declining (Garavello *et al.*, 2010), the incidence of oropharyngeal tumors is on the rise (Chaturvedi *et al.*, 2008; Marur *et al.*, 2010; Shiboski *et al.*, 2005). Oral cavity and oropharynx tumors are much more common in men and in the elderly population. The most significant risk factors for oral cavity and oropharyngeal tumors are tobacco and alcohol abuse (Blot *et al.*, 1988; Hashibe *et al.*, 2009). The rise in the incidence of oropharynx cancers, however, is mostly seen in the non-smoker, non-drinkers. This rise is currently associated with the infection with Human Papilloma Virus in the oropharyngeal tissues (Hammarstedt *et al.*, 2006). The main treatment for oral cavity tumors is surgical excision followed by radiotherapy or chemoradiotherapy in advanced cases. Oropharyngeal tumors on the other hand, are treated by definitive chemoradiation for the most part and surgery is reserved for salvage situations. The treatment of head and neck cancers has improved over the past few decades. The cure rates for early stage oral cavity, oral cavity and larynx cancers can reach as high as 70-80%. The advanced stage cancers still impose significant challenges on the treating physicians and the best outcomes are in the 40-50% range. Oropharyngeal cancers, especially in non-smokers, non-drinkers, can be cured with high degree of success even in relatively advanced cases (Ang *et al.*, 2010).

As is evident by the demographics of the head and neck cancer patients, this is a population prone to sleep disorders and especially OSA. Similar to head and neck cancers, OSA is more common in men, elderly and alcohol and tobacco abusers (Young *et al.*, 1993). In addition, most treatments of the head and neck cancers involve surgical resections, which alter the anatomy of the upper respiratory tract; or radiotherapy, that causes xerostomia and fibrosis; both known factors in causing or worsening OSA. As the survival of head and neck cancer patients has improved, practitioners have paid more attention to the quality of life measures and functional outcomes of the treatment of cancer patients. The cancer research community, therefore, has found new interest in identifying and studying sleep disorders in cancer survivors, as an important component of quality of life parameters. In spite of the importance of sleep in the quality of life of cancer survivors, the published literature on this topic is extremely limited. Most reports are

single institutional reports with a very small number of subjects. Even with this preliminary data, the picture is quite alarming. Sleep disorders are prevalent and severe in head and neck cancer patients. They tend to persist and even worsen after treatments. Unfortunately, most effective treatments are usually not accepted or tolerated by the patients. In the following chapter, we discuss the prevalence, impact, and extent of sleep disorders in head and neck cancer patients. We will describe and examine the available data on the diagnosis and treatments of sleep disorders in the cancer patients and finally study the impact of sleep disorders on the survival of the patients.

25.2 Clinical anatomy

A thorough understanding of the anatomy of the head and neck region is an essential prerequisite for all the practitioners in this field. Head and neck cancers are classified separately, and will behave differently based on their location in the upper aerodigestive tract.

The upper aerodigestive tract is divided into: nasal cavity and paranasal sinuses, oral cavity, pharynx, larynx and cervical oesophagus (Figure 25.1).

The oral cavity is defined as the space between the vermillion border of the lips and the junction of hard and soft palate superiorly and circumvallate papillae inferiorly. This space is further subdivided into the vestibule of the mouth (the space between the cheeks and the teeth) and the oral cavity proper. The vestibule includes the lips and buccal mucosa. Cancers of lips and buccal mucosa are common in pipe smokers and tobacco or betel nuts chewers respectively. The oral cavity proper is divided into: alveolar ridge, floor of the mouth, retromolar trigone, hard palate and oral tongue. The most common cancer of the oral cavity is squamous cell carcinoma of the oral tongue.
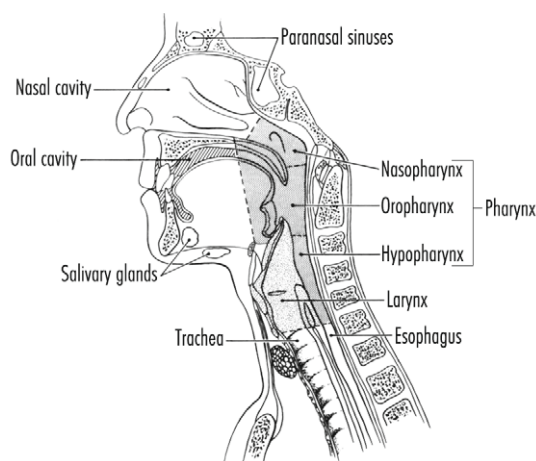
Figure 25.1. Sagittal section of the upper aerodigestive tract (Vokes *et al.,* 1993; reprinted with permission from New England Journal of Medicine. Copyright 1993 Massachusetts Medical Society).

The pharynx is a muscular tube that connects the nasal cavity and oral cavity (superiorly and anteriorly) to the larynx and cervical oesophagus (inferiorly). The pharynx is divided into: nasophayrnx, oropharynx, and hypopharynx. The oropharynx is defined as the space between the nasopharynx superiorly at the posterior border of soft palate, to the larynx and hypopharynx inferiorly at the dorsum of the base of tongue and glossoepiglottic folds. The oropharynx consists of: base of tongue, vallecula, soft palate, faucial arches, palatine tonsils, palatine fossa, and posterior pharyngeal wall. Most common tumors of the oropharynx are tonsillar carcinomas followed by base of tongue cancers. Cancers of soft palate and posterior pharyngeal walls are less frequent.

25.3 Principles of head and neck cancer treatment

In order to understand the relationship between sleep disorders and head and neck cancers a brief overview of the treatment modalities used for these diseases can be helpful. The general principle is to treat early stage disease with one modality and reserve multiple modalities for advanced disease or disease with high risk of recurrence. The main modalities of treatment are surgery, radiation and chemotherapy.

Oral cavity cancers are primarily squamous cell carcinomas. These cancers occur overwhelmingly in tobacco abusers and heavy alcohol abusers. The treatment of choice for most oral cavity cancers is primary surgical excision of the lesion. Removal of the cervical lymph nodes (neck dissection) is usually attempted at the time of the excision of the primary tumor, since oral cavity cancers metastasize to the regional lymph nodes in the neck quite frequently. After surgical excision, if there is evidence of metastatic disease in the neck, or the primary tumor is considered high risk for recurrence (positive surgical margins, large tumors, aggressive histopathology) patients will undergo radiotherapy to the primary site and the neck. If the disease in the neck shows adverse features such as extracapsular extension of the disease, chemotherapy will be added to the radiation.

Oropharyngeal cancers are also more common in tobacco and alcohol abusers, however, as mentioned earlier a group of non-smokers, non-drinkers, younger patients are nowadays afflicted with oropharyngeal cancers. In this group, infection with Human Papilloma Virus (especially types 16 and 18) has been associated with increased risk of cancer. The primary treatment of oropharyngeal cancers currently, is definitive concurrent chemoradiation. The main advantage of this approach is to avoid surgical excision that comes with increased morbidity due to difficult access and the loss of function of oropharynx. Surgical excision is usually reserved for recurrent cases and salvage situation after failure of chemoradiation.

One of the distinctive features of surgical excision of the head and neck cancers is the use of free tissue transfer to repair the defect. In these types of operations, after removing the tumor, the ensuing ablative defect will be filled with a vascularized viable cutaneous, fasciocutaneous, myocutaneous or osteocutaneous free flap. Free flap reconstruction is one of the major

advancement in the field of head and neck oncology and has made excision of large composite tumors possible with excellent functional results and diminished morbidity. The downside of free tissue transfer is that it replaces sensate, mobile native tissues with insensate, immobile, adynamic transplants. Therefore, it is not difficult to understand why patients can have significant changes in their physiologic functions such as breathing, swallowing and speech afterward (Figure 25.2). Furthermore, postoperative radiation and chemotherapy will cause significant fibrosis, xerostomia and sensory changes that can further hamper normal functioning. Consequently, a critical function such as maintaining a patent airway during sleep can be significantly affected by the disease and its treatments, hence the high prevalence of sleep disorders in these patients.
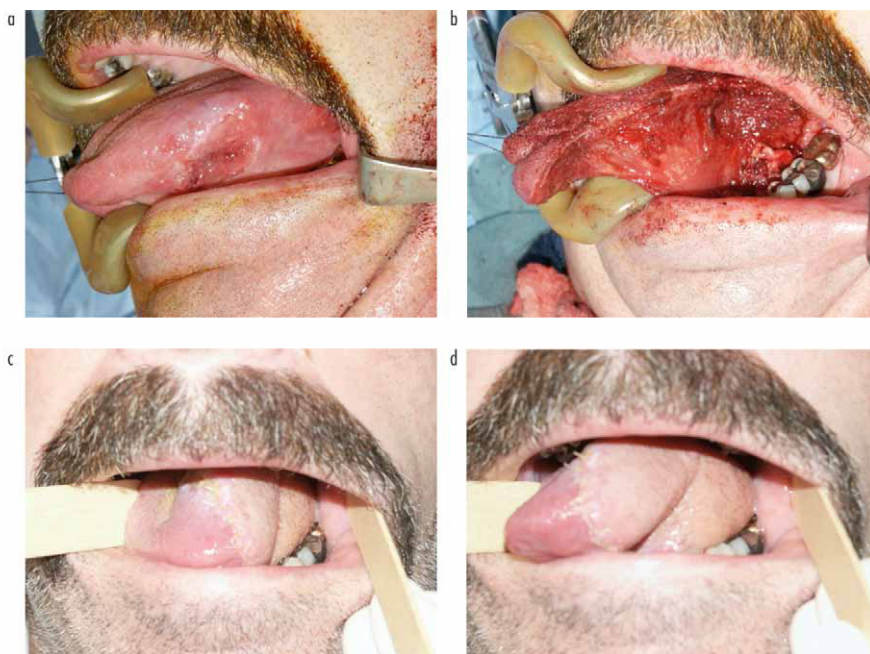
Figure 25.2. Surgical treatment of tongue cancer: The patient illustrated here is treated for oral tongue squamous cell carcinoma with surgical excision and radial forearm free flap. (a) Tumor before excision. (b) Resultant defect after complete removal of the tumor. Note that almost half of the oral tongue is missing. This defect requires free tissue transfer reconstruction. (c) and (d) View of the repair 6 weeks after the operation. Note that the free tissue transfer has provided adequate bulk to maintain the shape of the tongue, however, the mobility is somewhat affected and the transferred tissue is not sensate.

25.4 Epidemiology

An estimated 263,900 new cases and 128,000 deaths from oral cavity and oropharynx cancers occurred in 2008 worldwide. Central and eastern Europe has the third highest incidence behind Melanesia and South-Central Asia (Jemal *et al.*, 2011). The overall incidence and mortality of oral cavity cancers is decreasing in most geographical regions, however, the incidence of oropharyngeal cancers is on the rise. The decline in the oral cavity cancers is mostly related to the declining smoking rates among adults in different communities. The rise in oropharynx cancers, on the other hand, is believed to be associated with HPV infection in the oropharynx. HPV is a sexually transmitted disease and is believed to be an independent risk factor in the development of oropharyngeal cancers. Alcohol consumption, poor dental hygiene and diets low in fresh fruits and vegetables are among other risk factors for development of oral cavity and oropharynx cancers.

The incidence of obstructive sleep apnea in general public is reported around 9% for males and 4% for women (Young *et al.*, 1993). The definitions, symptoms and deleterious effects of OSA are well described elsewhere in this handbook. The incidence of OSA in head and neck cancer patients is rarely studied and described. The incidence of sleep disorders can be studied in two stages: First, the prevalence of sleep disorders after diagnosis, and before definitive treatments. Second, the prevalence after completion of treatment and during the follow up period among survivors. Ideally, patients should be followed longitudinally to determine the prevalence, before and after treatment, to study the effects of disease and treatments, separately.

The incidence of sleep disorders and specifically OSA, before treatments, has been studied in a few reports. A study of 17 patients with oral cavity and oropharynx cancers before surgical excision showed a very high prevalence of OSA in this group. Payne *et al.* reported an incidence of 76%, using polysomnography (Payne *et al.*, 2005). In addition, 77% of patients with OSA had an apnea-hypopnea index of more than 40, indicative of severe sleep apnea. The authors could not identify any significant differences between patients with and without OSA, which is not surprising considering the small size of the cohort. Head and neck cancer patients also show a lower score in subjective sleep assessment questionnaires. A study by Duffy *et al.* showed lower scores for the head and neck cancer patients before treatment than the general public (2008). In this group, younger age, smoking, low levels of physical activity and depression were associated with lower scores. Oral cavity cancer patients had better scores than oropharynx and larynx cancers.

The incidence of sleep problems after treatment is equally high if not higher. More studies exist on the incidence of sleep problems in this group of patients. One of the first studies to address this specific question was reported by Friedman *et al.* in 2001. He reported an incidence of 91.7% in a group of 24 patients with oral cavity, oropharynx and larynx cancers. All patients had been successfully treated and had no evidence of disease at the time of sleep studies. This study marks the highest reported incidence of OSA in treated cancer patients. Because of the small number of patients, no significant factor was identified. Subsequently a few more studies have

shown significantly higher incidence of OSA in treated head and neck cancer patients, however, none showed a rate as high as Friedman's report (Israel *et al.*, 2006; Qian *et al.*, 2010; Nesse *et al.*, 2006; Rombaux *et al.*, 2000; Steffen *et al.*, 2009). Table 25.1 describes the available studies on the incidence of OSA after treatment. The reported incidence can be as low as 8% and as high as 91.7%.

In terms of subjective quality of sleep after treatment, the available studies again show lower scores for head and neck cancer patients (Duffy *et al.*, 2008; Shuman *et al.*, 2010). Head and neck cancer patients continue to experience inferior quality of sleep after completion of treatments. Interestingly, the quality of sleep did not show any improvement from the baseline levels in one study (Duffy *et al.*, 2008; Shuman *et al.*, 2010).

25.5 Predisposing factors

No single persistent risk factor has been associated with OSA in cancer patients. Usual risk factors in general population such as body mass index and age, are not significant in head and neck cancer patients (Qian *et al.*, 2010). In fact, lower quality of sleep scores is more common in younger cancer patients than older patients (Duffy *et al.*, 2008; Rogers *et al.*, 2008). No specific site also been associated with higher incidence, but a few studies report higher incidence in Hypopharynx and larynx tumors than tumors of oral cavity (Duffy *et al.*, 2008; Steffen *et al.*, 2009). In one study, a history of transient tracheostomy during treatment was associated with higher rate of OSA (Steffen *et al.*, 2009), however, other studies did not find this factor significant (Rogers *et al.*, 2008). Patients who were treated with radiotherapy consistently show high incidence of OSA. But no study have been able to show a difference in the rate of OSA between patients who were treated by radiotherapy versus surgery alone (Friedman *et al.*, 2001; Qian *et al.*, 2010).

In two studies by University of Michigan, sleep problems were associated with younger age, pain, depression, xerostomia, presence of tracheostomy tube, and other co-morbidities. Smoking, problem drinking and female sex were also marginally significant (Duffy *et al.*, 2008; Shuman

Table 25.1. Available studies on the incidence of obstructive sleep apnea in head and neck cancer patients.

Study	Number of subjects	Primary site	Incidence
Rombaux *et al.* (2000)	40	larynx	3 (8%)
Friedman *et al.* (2001)	24	oral cavity, oropharynx, larynx	22 (91.7%)
Nesse *et al.* (2006)	33	oral cavity, oropharynx	4 (12%)
Israel *et al.* (2006)	22	larynx	19 (86.3%)
Steffen *et al.* (2009)	31	oral cavity, oropharynx, larynx	6 (19%)
Qian *et al.* (2010)	24	oral cavity, oropharynx	14 (58.3%)

et al., 2010). In these studies the modality of treatment was not a predictor of quality of sleep. Patients who were treated with radiotherapy or surgery or chemotherapy have similar sleep scores.

The role of tracheostomy in sleep disorders is worthy of mentioning. Tracheostomy is considered as one of the definitive treatments of OSA. In most studies of prevalence of OSA in head and neck cancers, patients with tracheostomy were excluded. In at least one study, patients with a history of prior tracheostomy showed higher incidence of OSA (Steffen *et al.*, 2009). This finding has not been duplicated in other reports. Tracheostomy was also identified as a significant factor in subjective quality of sleep in Michigan studies (Shuman *et al.*, 2010). Patients with tracheostomy had significantly lower sleep scores. In contrast, in a study by Rogers, presence of tracheostomy was not a significant factor (Rogers *et al.*, 2008).

In summary, subjective sleep quality and OSA are common in head and neck cancer patients. Patients with oropharynx tumors might have a higher incidence of OSA and lower quality of sleep scores. Significant factors in the quality of sleep are younger age, depression, pain, xerostomia and other co-morbidities. Tracheostomy might be a factor in lower quality of sleep. No single factor is associated with higher incidence of OSA in these patients, but the available data is very limited.

25.6 Diagnosis

In general, approach to head and neck cancer patients starts with a detailed history and directed physical exam. Asking sleep related questions in the history can direct the physician to more in depth investigation of sleep problems. Formal questionnaires have been developed and validated, that can enhance the efficiency of history taking immensely. Detailed physical exam of the head and neck region coupled with office based fibreoptic flexible nasopharyngolaryngoscopy can provide valuable information in the diagnosis of sleep apnea. Obvious deformities of nasal septum, large protruding masses, and vocal cord paralysis can be identified and further investigated. In patients with prior radiation, attention to the degree of xerostomia is important; since xerostomia can cause and aggravate sleep problems (Jellema *et al.*, 2007; Rada, 2005). Radiographic studies are almost routinely obtained in the work up of the patients. These studies, in particular, magnetic resonance imaging (MRI), and computed tomography (CT) scan of the head and neck can provide detailed anatomic images that can identify alterations in the structure of the air passages (Figure 25.3).

Investigating sleep problems is not part of the routine diagnostic work up of cancer patients currently. This routine might soon change as more data is accumulated on this topic and importance of sleep in the outcome of cancer patients is elucidated. Most diagnostic work up is done in the context of research projects and only a few centers screen cancer patients routinely.

The first step usually involves a self administered questionnaire. Common questionnaires used in determining sleep problems are: ESS (Johns, 1991); MOS questionnaire (Hays *et al.*, 1995)
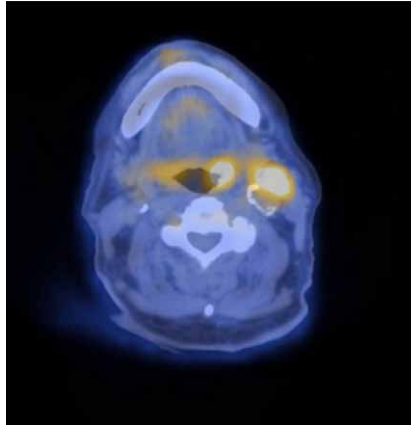
Figure 25.3. Combined positron emission tomographay-computed tomography (PET-CT) scan of tonsil cancer with lymph node metastases. Please note that both primary tumor and lymph node metastases are identified by PET-CT. The preferred method of treatment in this case is definitive chemoradiation. These patients are at risk for xerostomia and resultant sleep disorders.

and EORTC-QLQ-C30 (Aaronson *et al.*, 1993). Many studies have designed their own in house questionnaire to investigate sleep problems.

The ESS is a simple self administered questionnaire that assesses the general level of daytime sleepiness (Johns, 1991). The questionnaire asks the individuals to rate their likelihood of falling sleep in eight common daily situations. ESS scores range from 0 to a maximum of 24. A score of more than 10 is usually consistent with excessive daytime sleepiness. Total ESS score reliably distinguishes normal individuals from patients with sleep apnea, narcolepsy and other disorders of sleep such as idiopathic hypersomnia. ESS has been used in a few studies of sleep disorders in head and neck cancer patients with mixed results (Israel *et al.*, 2006; Nesse *et al.*, 2006; Qian *et al.*, 2010; Steffen *et al.*, 2009). In a study by Nesse *et al.* (2006), ESS was used as a screening tool to identify the patients at risk for OSA. In this study, four out of 10 patients with high ESS scores were confirmed to have OSA on polysomnography. However, in studies that have tried to correlate the ESS score with the existence of OSA in the head and neck cancer patients, the results are disappointing. In studies by Steffen *et al.* (2009), Israel *et al.* (2006) and Qian *et al.* (2010), ESS scores did not predict the presence of OSA in patients. In all three studies the prevalence of OSA was much higher than one could have suspected based on the total ESS score. Therefore, a high ESS score should be investigated further, however, a low score cannot reliably rule out OSA.

One of the other commonly used questionnaires is QLQ-C30, designed by the EORTC (Aaronson *et al.*, 1993). This questionnaire is intended to be used with site specific modules. The EORTC head and neck module is 'QLQ-H&N35'. There is only one question on QLQ-C30 form about sleep: 'During the past week, have you had trouble sleeping?' Interestingly, there are no questions on sleep in the 'QLQ-H&N35'. This questionnaire can be used as a screening tool in context of quality of life assessment, to identify patients with potential sleep problems.

MOS sleep measure represents four constructs that are related to sleep quality: sleep disturbance; adequacy of sleep; somnolence; and respiratory problems (Hays *et al.*, 1995). This questionnaire has been validated in a large sample of chronically ill patients and in patients enrolled in clinical trials. The short form of the questionnaire includes six questions. The MOS sleep measure was used in studies by University of Michigan to identify sleep problems in head and neck cancer patients (Duffy *et al.*, 2008; Shuman *et al.*, 2010).

Many other studies have designed their own specific questionnaires to investigate the prevalence and nature of sleep problems in these patients (Friedman *et al.*, 2001; Nesse *et al.*, 2006; Steffen *et al.*, 2009). No single questionnaire has been shown to be highly reliable in detecting OSA in head and neck cancer patients. This can be due to the belief of many patients that their symptoms are not related to sleep but to cancer and its treatments. Nonetheless, valuable information can be obtained from these questionnaires and their use is becoming more common in both research and clinical settings.

Similar to the general population, the gold standard test in diagnosing sleep apnea in head and neck cancer patients is polysomnography. Performing polysomnography in cancer patients is not an easy task. In the pretreatment periods, patients are experiencing heightened levels of anxiety, fear and depression. In addition, most patients are undergoing different diagnostic tests in preparation for surgical or radiation treatments. Some are overly symptomatic and cannot tolerate polysomnography. As mentioned earlier, the data on prevalence of OSA pretreatment is currently limited to only one study involving 17 patients (Payne *et al.*, 2005). Performing polysomnography after completion of treatments is not as prevalent either. The acceptance of polysomnography among survivors is generally low and the cost and effort that is involved in performing this test are also prohibitive in many settings. Most reported series, again, have a very low number of participants and most do not report how many patients declined participation. In a study performed by the senior author, out of 59 patients who were approached, only 24 accepted to participate (40%) (Qian *et al.*, 2010). This low number is not at all surprising to practitioners familiar to specific characteristics of head and neck cancer patients. Head and neck cancer and specifically oral cavity cancer afflicts patients from lower socioeconomic classes disproportionately. Long term follow up of the patients, let alone involvement of a large proportion in research studies and additional tests, can be particularly difficult.

In summary, diagnosis and work up of sleep problems in head and neck cancer patients is mostly limited to research projects. The most common tools are self administered questionnaires to identify symptoms of sleep problems and particularly OSA followed by polysomnography in appropriate, willing patients.

25.7 Treatment

The data on the treatment of sleep disorders in head and neck cancer patients is extremely limited. Head and neck cancer patients impose a particularly challenging group of patients to

treat. Most have had surgical procedures that have altered the upper aerodigestive tract anatomy. The majority have undergone radiotherapy which causes fibrosis and stiffness of the tissues and also significant levels of xerostomia.

The first step in addressing sleep problems in head and neck cancer patients is to change the attitude of the patients and treating practitioners. Most patients and physicians are unaware of the prevalence of sleep problems and its deleterious effects. Many patients, mistakenly, consider the fatigue and lack of energy, due to poor quality of sleep as an inevitable consequence of cancer and treatments. A systematic approach to addressing sleep problems can bring tremendous benefits to the patients, their overall quality of life, and may be even prolong survival (Osthus *et al.*, 2011).

After identifying the presence of sleep problems, the first step is to search and treat common associated conditions. Similar to most cancer patients, head and neck patients are afflicted with a list of common problems. Pain is a major problem in head and neck cancer patients. Adequate treatment of pain is an essential prerequisite in addressing sleep problems. Many treatments are available. These can be as simple as prescribing the appropriate and adequate amount of pain medication to an expedited referral to a multidisciplinary pain clinic. Pain should be adequately treated in all cancer patients if there is any expectation of improving the quality of life in survivors. The second common problem in head and neck cancer patients and cancer survivors in general is mood disorders, and in particular major depression. The presence of depression has been linked to the poor quality of sleep in the head and neck cancer patients, and is a major somatic symptom in this population (Shuman *et al.*, 2010). Patients should be interviewed carefully by experienced practitioners to identify symptoms of depression and offered adequate treatments. Many antidepressants, however, have an anticholingergic side effect profile that can worsen the pre-existing xerostomia. Attention to this point in head and neck cancer patients is particularly important and one should consider medications that have the most favourable side effect profile. Other associated factors that can affect sleep in patients are smoking and alcohol abuse. Up to 20% of patients continue to smoke or abuse alcohol after diagnosis (Duffy *et al.*, 2008). Effective counseling and appropriate interventions are proven to help the patients in overcoming these difficult addictions.

Head and neck cancer patients suffer from a specific set of problems additionally. Many patients have undergone radiation to the neck or operations that remove the entire thyroid gland or a major part of it. These patients, therefore, are prone to hypothyroidism and myxoedema. Myxoedema is a known risk factor for sleep apnea (Grunstein and Sullivan, 1988; Rajagopal *et al.*, 1984). Thyroid function test should routinely be monitored in all patients who have a history of radiation to the neck or previous thyroidectomy, and adequate replacement should be administered when necessary. Presence of tracheostomy and feeding tubes has been associated with poorer quality of sleep (Shuman *et al.*, 2010). All patients should be assessed frequently to determine the necessity of maintaining tracheostomy or feeding tubes if present, and ideally should be discontinued as soon as safely possible. However, before discontinuing these measures, the risks and benefits should be carefully weighted. Removing feeding tubes prematurely can put the patients at risk of aspiration and malnutrition. Tracheostomies are even more delicate to address. Tracheostomy is

an accepted treatment for obstructive sleep apnea. However, in multiple studies of head and neck cancer patients, those with a tracheostomy tube report a substantive decrease in overall quality of life, and specifically a lower quality of sleep. The decision to maintain or remove a tracheostomy should be made carefully and only after considering many factors such as the security of the airway and the possible increased risk of obstructive sleep apnea. In general, tracheostomy should be removed as soon as the patient can maintain an adequate and safe airway (Qian *et al.*, 2010).

Xerostomia is another common and specific problem to head and neck cancer patients. The severity of xerostomia has been decreased by the adoption of intensity modulated radiotherapy (Graff *et al.*, 2007) in which the parotid glands are usually spared significant radiation dose. Unfortunately, most of the basal level (70%) of saliva and mucous secretion is produced by the submandibular (Stuchell and Mandel, 1988) glands. These glands are almost always affected by surgery or radiation. Consequently, a significant number of patients complain and suffer from xerostomia post treatment. Mucins bind water effectively and keep the mucosal surfaces hydrated. In addition, they help to reduce the surface tension, thus reduce the tendency of functional narrowing of the upper aerodigestive passages by inhibiting surface tension-mediated mucosal fold apposition (Amerongen and Veerman, 2002; Kirkness *et al.*, 2003). Adequate hydration can reduce these symptoms to some degree. Overzealous drinking of fluids on the other hand may cause polyuria and nocturia that can further disrupt a healthy sleep cycle, and potentiate lymphedema. Adding humidity to the ambient environment is also quite beneficial. Asking specifically about the living conditions can identify common dry climates such as air conditioned rooms, or overly heated residences during cold winter months. Many patients will benefit by installing a humidifier next to their bed to avoid mucosal dryness during sleep hours. Finally, topical use of mucin-like sprays into upper respiratory tract can decrease intraluminal pressure that is required to reopen a closed pharyngeal airway and could reduce the severity of sleep apnea (Momm and Guttenberger, 2002; Morrell *et al.*, 2002).

Treating sleep apnea in head and neck cancer patients is specially challenging. The therapeutic options are limited, since majority of patients cannot undergo definitive surgical procedures or other invasive interventions. Most patients already have undergone surgical procedures, radiation or chemotherapy that has altered upper airway's anatomy and pliability. Radiated tissues have significantly lower capacity for recovering from surgical wounds and procedures. Understandably, many specialists are reluctant to offer any surgical procedures to address sleep apnea. Prescribing CPAP treatment has also not found that much success. A significant number of patients will find the treatment intrusive and too cumbersome to use and will not apply it on a regular basis (Qian *et al.*, 2010). Patients who have undergone extensive surgical procedures cannot be fitted with CPAP machines easily. All these factors have led to very low compliance with CPAP use in this population. Nevertheless, the benefits of CPAP treatments are well documented and the practitioners should identify and encourage the appropriate patients to use this effective therapy.

In summary, treatment of sleep disorders and sleep apnea in head and neck cancer patients is difficult. Therapeutic options are limited and not always effective or acceptable. The best results are achieved in a multidisciplinary setting by participation of different specialists. A systemic

approach to identify and address all the different problems that these patients face, has the best chance of success. Treating pain, depression, substance dependence, hypothyroidism, and xerostomia can all improve the quality of sleep. Assessing the need for tracheostomy and feeding tubes and removal when appropriate should be attempted. Finally, using CPAP, whenever possible, should be encouraged and tried. The patients and practitioners will be surprised that how much the overall quality of life can be improved by treating sleep problems. Figure 25.4 describes an algorithm for the diagnosis and treatment of sleep problems in head and neck cancer patients.

25.8 Impact of sleep problems on survival

The ultimate quest for every cancer patient and provider is improving survival. The survival of head and neck cancer patients has improved only modestly in the past several decades. Advanced stage head and neck cancer still carries a 50-60% five-year survival prognosis. Apart from known risk factors that decrease survival such as tobacco abuse, advanced age, advanced disease, and lower socioeconomic status not that many other factors have been identified. Higher overall quality of life scores in surveys have been associated with better survival (Karvonen-Gutierrez
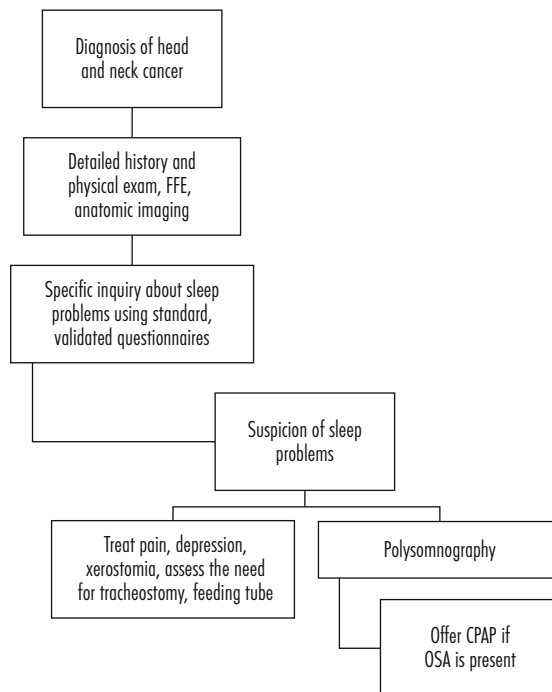
Figure 25.4. Approach to diagnosis and management of sleep problems in head and neck cancer patients. No single standard, universal questionnaire exists. The choice is dependent on the practitioner's preference.
FFE = fiberoptic flexible endoscopy; OSA = obstructive sleep apnea; CPAP = continuous positive airway pressure.

et al., 2008). The data on the impact of sleep problems on survival of head and neck cancer patients is extremely limited. In one report by University of Michigan group, sleep disturbance was not a significant factor in overall survival of more than 500 patients in the study (Duffy *et al.*, 2009). In this study the most significant factors were smoking, low dietary fruit intake, advanced age and lower education levels. In a small study of prevalence of OSA in head and neck cancer patients before treatment, those who were diagnosed with OSA had longer operative time, more cardiopulmonary complications, increased mechanical ventilation requirements and longer intensive care unit stays (Payne *et al.*, 2005). Due to the small number of participants, none of these differences reached statistical significance, however a trend toward increased perioperative morbidity was observed in patients with OSA.

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Summary points

- Hypnotics could precipitate sleep-related eating disorder (SRED) in subjects with predisposing medical or environmental factors.
- Zolpidem, among all drugs, seems to have a prominent inducing effect, as was seen in most of the reviewed cases.
- Before initiating medication, subjects should be carefully screened for presence of predisposing factors, such as comorbid obstructive sleep apnea (OSA), restless legs syndrome (RLS), sleepwalking, poor sleep hygiene, and previous history of eating disorder.
- The frequency of SRED and latency between the onset of SRED and the use of hypnotics are variable; therefore, the presence of SRED should be regularly checked during pharmacologic therapy for insomnia.

26. Sleep-related eating as a side effect of drugs for insomnia

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Abstract

Sleep-related eating disorder (SRED) is defined by the amnestic eating behavior during sleep. Recently several peer reviewed case reports of SREDs have emerged in the medical literature with emphasis on concurrent use of hypnotics. The characteristics of hypnotic-related SRED can be summarized as sleepwalking, incomplete arousal, and compulsive eating behavior after the exposures to hypnotics. In this chapter, the authors reviewed existing case reports, summarized the findings, and suggested the mechanisms and management of hypnotic-related SRED. Most commonly reported hypnotic in these reports was zolpidem. Zolpidem was assumed to induce SRED based on the close temporal relationship between SRED manifestations and the initiation or change of the drug ingestion, and the resolution of symptoms after withdrawal, dose reduction, or formulation change. Across the reviewed cases, prescribed zolpidem dose was usually within the recommended range, but the latency to the development of SRED after the exposure and the frequency of symptoms were variable. Age-related vulnerability or gender predilection was not documented. History of prior eating disorder as well as co-existing sleep disorders (obstructive sleep apnea (OSA) and restless legs syndrome (RLS)) were common, and these were identified as predisposing factors along with poor sleep hygiene as well as a history of sleepwalking. It is thus recommended to screen these predisposing factors before initiating hypnotics in patients who are suffering from insomnia. Additionally, the presence of SRED should be regularly checked during the pharmacologic therapy for insomnia.

Keywords: zolpidem, eszopiclone, zaleplon, ramelteon, adverse events, sleepwalking, restlesslegs syndrome, sleep apnea, dopamine, gamma-aminobutyric acid

Abbreviations

GABA   Gamma-aminobutyric acid
OSA   Obstructive sleep apnea
RLS   Restless legs syndrome
SRED   Sleep-related eating disorder

26.1 Introduction

Sleep-related eating disorder is characterized by recurrent episodes of involuntary eating and drinking during the main period of sleep (Schenck *et al.,* 1991; Winkelman, 1998). Patients ingest abnormal combination of food or inedible substances during the events and are vulnerable to weight gain and obesity (Schenck *et al.,* 1991; Winkelman, 1998). It is also common for patients to complain of non-restorative sleep, daytime fatigue or somnolence, and morning flatulence or anorexia that result from night-time activities. Consciousness is usually impaired during the event. Patients are fully or partially amnestic about their night-time behaviors and are prone to physical injuries such as falls, burns, and cuts, which could happen during the searching or preparation activities related to food (Schenck *et al.*, 1993; Schenck and Mahowald, 1994, 2000). Amnesia for the events is regarded as a differentiating feature of SRED from nocturnal eating syndrome (O'Reardon *et al.*, 2005; Schenck *et al.*, 1991, 1993; Winkelman, 1998). However the diagnostic criteria for SRED in the revised edition of *International Classification of Sleep Disorders* do not specify the level of consciousness during night eating and the recollection of the events (Table 26.1). The categorical distinction between SRED and nocturnal eating syndrome would be compromised by the revised criteria. Therefore, SRED in this chapter will be defined as amnestic

Table 26.1. Diagnostic criteria for sleep-related eating disorder (American Academy of Sleep Medicine, 2005).

A.   Recurrent episodes of involuntary eating and drinking occur during the main sleep period.

B.   One or more of the following must be present with the recurrent episodes of involuntary eating and drinking:
   1. consumption of peculiar forms or combinations of food or inedible or toxic substances;
   2. insomnia related to sleep disruption from repeated episodes of eating, with a complaint non restorative sleep, daytime fatigue, or somnolence;
   3. sleep-related injury;
   4. dangerous behaviors performed while in pursuit of food or while cooking food;
   5. morning anorexia;
   6. adverse health consequences from recurrent binge eating of high caloric food;

C.   The disturbance cannot be better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use or substance use disorder.

eating behavior during sleep. The reported prevalence of SRED is variable, ranging from 0.5% to 27%, depending on the character of sample population and the definition of SRED (Lam *et al.*, 2008; Rand *et al.*, 1997; Schenck *et al.*, 1991, 1993; Winkelman, 1998). The prevalence was 2.4% in adults with psychiatric disorders, 4.6% in college students and 8.7% in subjects with eating disorder (Lam *et al.*, 2008; Winkelman, 1998). As for now the prevalence in the general population is unknown, but female predominance and genetic influence can be assumed from previous studies.

Pathophysiology is unclear, but it is hypothesized that SRED shares a mechanism with somnambulism (sleepwalking), both of which are associated with partial arousal during sleep. While other parts of brain remain sleeping, selective or susceptible regions of the brain area are aroused to a level that induce behavioral symptoms, such as walking, searching or cooking food, and eating. As a result, patients with SRED or somnambulism often exhibit inappropriate behaviors or responses during the events but report no or partial recollection of their activities after they are fully awake. Preceding alcohol ingestion, partial sleep deprivation, and hypnotic use have been previously recognized as precipitating factors for somnambulism, because they increases subjects' vulnerability to partial or incomplete arousals (Liskow and Pikalov, 2004; Yang *et al.*, 2005). Therefore it is plausible that those factors can also contribute to the development of SRED.

Recently peer reviewed case reports describing SRED concurrent with hypnotic use have appeared in the medical literature (Adverse Drug Reaction Advisory Committee, 2007; Chiang and Krystal, 2008; Dang *et al.*, 2009; Hoque and Chesson, 2009; Menkes, 1992; Miranda *et al.*, 2010; Molina and Joshi, 2010; Morgenthaler and Silber, 2002; Najjar, 2007; Sansone and Sansone, 2008; Schenck *et al.*, 1991, 1993; Valiensi *et al.*, 2010; Wing *et al.*, 2010; Yun and Ji, 2010). In this chapter, the authors aimed to (1) summarize the clinical features of the published cases with hypnotics-related SRED, (2) discuss the possible mechanisms, and (3) suggest the treatment strategy. The focus will be placed on the review of SRED associated with non-benzodiazepine receptor agonists (zolpidem, [es]zopiclone, zaleplon) because these drugs are widely prescribed for the treatment of insomnia.

26.2 Hypnotic-related sleep-related eating disorder

The sedative-hypnotic drugs have a potential to evoke complex sleep-related behaviors. In 2007 the US Food and Drug Administration requested all the manufacturers of sedative-hypnotic drugs to add warnings to their labels and indicate the risk of amnestic behaviors during sleep including sleep-driving, making phone calls, and sleep-related eating (US FDA, 2007). Thirteen drugs that are subjected to these risks are specified in the list (Table 26.2). Among them, three drugs have been related to SRED: zolpidem (Adverse Drug Reaction Advisory Committee, 2007; Chiang and Krystal, 2008; Dang *et al.,* 2009; Hoque and Chesson, 2009; Miranda *et al.,* 2010; Morgenthaler and Silber, 2002; Najjar, 2007; Sansone and Sansone, 2008; Valiensi *et al.,* 2010; Wing *et al.,* 2010; Yun and Ji, 2010), zaleplon (Molina and Joshi, 2010), and triazolam (Menkes,

Table 26.2. List of 13 sedative-hypnotic drugs with a potential to induce complex sleep-related behaviors (US FDA, 2007).

zolpidem[1] (both conventional and continuous-release form)

butabarbital

pentobarbital and carbromal

flurazepam

quazepam

triazolam[1]

eszopiclone

ethchlorvynol

estazolam

temazepam

ramelteon

secobarbital sodium

zaleplon[1]

[1] The association with sleep-related eating has been reported in the medical literatures.

1992; Schenck *et al.,* 1991, 1993). However, lack of reports on other drugs does not necessarily place the three drugs as the sole, most potent contributors that provoke SRED. Some psychotropic medication, including olanzapine, risperidone, and amitriptyline, are also known to associate with SRED (Lu and Shen, 2004; Paquet *et al.,* 2002; Schenck *et al.,* 1993). The actual risk and the drug specificity of hypnotic-related SRED cannot be ascertained until well-designed comparative study or surveillance data become more readily available. Nonetheless, recent attention has been focused on zolpidem, a drug that was indicated as a causative factor in 10 of the 11 reports on the hypnotic-related SRED (Chiang and Krystal, 2008; Dang *et al.,* 2009; Hoque and Chesson, 2009; Miranda *et al.,* 2010; Molina and Joshi, 2010; Morgenthaler and Silber, 2002; Najjar, 2007; Sansone and Sansone, 2008; Valiensi *et al.,* 2010; Wing *et al.,* 2010; Yun and Ji, 2010). The Therapeutic Goods Administration of Australia issued warnings in 2007 with regard to SRED as a potential adverse effect of zolpidem (Adverse Drug Reaction Advisory Committee, 2007).

26.3 Zolpidem and sleep-related eating disorder: review of cases

The authors identified twenty case reports on zolpidem-related SRED from medical literatures written in English (Chiang and Krystal, 2008; Dang *et al.,* 2009; Hoque and Chesson, 2009; Morgenthaler and Silber, 2002; Najjar, 2007; Sansone and Sansone, 2008; Wing *et al.,* 2010; Yun and Ji, 2010). The incidence is unknown, though it may be reflected in the data on the overall hypnosedative-induced amnestic complex behaviors. About 1-5% of the subjects who were exposed to zolpidem experienced amnestic complex behaviors (Ganzoni *et al.,* 1995; Tsai *et al.,* 2009). The range of subjects' age was variable and no gender predilection was observed

(male, 51.7%; Table 26.3). There was no prior history of SRED in the subjects but the time interval between the onset of SRED and zolpidem initiation varied, ranging from days to years. Frequency of symptoms was also variable (nightly, weekly, monthly, or a few times a year). Most of subjects had been taking usual daily dose of zolpidem; the dose was 10 mg/day in 15 (75.0%), 6.25 mg in one, and 12.5 mg in two. Only two subjects had been taking high dose (20 and 30 mg, respectively). The role of formulation in zolpidem was evident in two subjects who developed SRED after changing from the immediate- (10 mg/day) to the controlled-release (12.5 mg/day) form. Subsequently, their disease symptoms were reversed by switching back (Chiang and Krystal, 2008). In most subjects (19 of 20, 95.0%), SRED disappeared after withdrawal (n=16), reduction (n=1) or changing the formulation with concomitant dose reduction (n=2) of zolpidem. One subject had residual SRED symptoms with the continued but dose-reduced use of zolpidem (Wing *et al.,* 2010). Nocturnal eating did not recur in one subject who took eszopiclone after the withdrawal of zolpidem (Najjar, 2007). Ten subjects were prescribed with benzodiazepine (clonazepam in seven, lorazepam in two, and temazepam in one) and symptoms did not recur (Morgenthaler and Silber, 2002; Wing *et al.,* 2010; Yun and Ji, 2010). Prior sleepwalking was present in only two (10.0%). History of eating disorder was specified in eleven subjects, and five (45.5%) had a history of daytime eating disorder. Co-existing sleep disorders were common, as seen in ten subjects who had RLS and thirteen subjects who had OSA. Polypharmacy with concurrent medication usage was also commonly seen; all except one had been taking 1-7 medications in addition to zolpidem. Antidepressants were prescribed in fourteen and dopamine agonist in five.

In summary, zolpidem was assumed to induce SRED based on the close temporal relationship between SRED manifestations and the initiation or change of zolpidem ingestion. Symptoms seemed to resolve after zolpidem was withdrawn, reduced, or altered in formation. Prescribed dose was usually within the recommended range. The latency to the development of SRED after the exposure to zolpidem and the frequency of symptoms varied between subjects. Prior sleepwalking history was rare (10.0%) but prior eating disorder (45.5%) as well as co-existing other sleep disorders (OSA, 81.3%; RLS, 55.6%) were common. Age-related vulnerability or gender predilection could not be determined from these observations, but SRED in general and clinic populations was presented with adolescent to young adulthood onset, female preponderance, higher prevalence (at least 50%) of sleepwalking, and chronic course lasting more than a decade (Schenck *et al.,* 1991, 1993; Winkelman, 1998).

26.4 Zolpidem and sleep-related eating disorder: risk factors and plausible mechanisms

As described above, sleep disorders, such as OSA and RLS, are highly prevalent in reported cases with zolpidem-related SRED (Table 26.3). Sleep apnea and RLS are common conditions affecting about 2-5% of the general population and cause significant sleep disruptions (Ferri *et al.,* 2010; Kimoff, 1996; Ohayon *et al.,* 2011; Young *et al.,* 1993). OSA is regarded as major risk for adult chronic sleepwalking (Guilleminault *et al.,* 2005), although previous history of sleepwalking was

Table 26.3. Characteristics of subjects with zolpidem-induced sleep-related eating disorders (SRED) reported in medical literatures.

Author	Number of cases	Age	Sex	Zolpidem dose (mg)	formulation	Previous history			Co-existing sleep disorders		
						SRED	other eating disorder	sleep-walking	RLS	OSA	PLMS
Morgenthaler and Silber (2002)	5	61.4±6.0 (54-67)	M: 3 F: 2	10.0±3.5 (5-15)	IR	no	2 (40%)	1 (20%)	5 (100%)	3 (60%)	1 (20%)
Najjar (2007)	1	46	F	6.25	CR	no	NS	no	present	present	NS
Chiang and Krystal (2008)	2	72.5±3.5 (70, 75)	M: 2	12.5	CR	no	NS	1 (50%)	2 (100%)	2 (100%)	NS
Sansone and Sansone (2008)	1	51	F	10	IR	no	no	no	present	NS	NS
Dang et al. (2009)	1	45	M	10	IR	no	NS	no	NS	NS	NS
Hoque and Chesson (2009)	1	51	M	10	IR	no	no	no	NS	present	NS
Wing et al. (2010)	8	49.9±14.6	M: 3 F: 5	10 (8 cases)	IR	no	3 (37.5%)	no	no	6 (75.0%)	no
Yun and Ji (2010)	1	45	M	10	IR	no	no	no	present	no	no

SRED = sleep-related eating disorder; RLS = restless legs syndrome; OSA = obstructive sleep apnea; PLMS = periodic limb movement during sleep; M = male; F = female; IR = immediate-release form; CR = continuous-release form; NS = not specified.

rare in the reviewed case series (Table 26.3). As documented in some cases, extrinsic factors such as alcohol ingestion or cessation of smoking could accentuate sleep instability (Wing *et al.,* 2010); therefore it could be hypothesized that any intrinsic (history of sleepwalking and co-existing sleep disorders) and extrinsic (alcohol, smoking) factors could predispose subjects to zolpidem-related SRED.

The second prominent characteristic is impaired consciousness during the event. Zolpidem, like other non-benzodiazepine receptor agonist such as zaleplon and (es)zopiclone, selectively acts on the GABA A receptor (particularly α1-GABA A subtype) that mediates sedative and amnestic effects. Complex behavior risk may increase with both dose and binding affinity at α1-GABAA receptors (Dolder and Nelson, 2008). The dose used in zolpidem-induced amnestic somnambulism has been reported to be higher than in control insomnia (Tsai *et al.,* 2009). The concomitant medication may also result in unintended increase of zolpidem concentration at the site of action (Dolder and Nelson, 2008). As summarized above, most of reported cases with SRED had been taking a significant number of concurrent medications which might increase the chance of unfavorable pharmacokinetic interactions. For example, the majority of antidepressants inhibits cytochrome P450 pathway, a main metabolic pathway of zolpidem (Dolder and Nelson, 2008). Furthermore, zolpidem has the highest receptor-binding affinity among the non-benzodiazepine receptor agonists, which may explain its more frequent association with hypnosedative-induced complex behavior (Dolder and Nelson, 2008). One report has issued on the reversal (or 'recuperation') of SRED by changing hypnotics from zolpidem to eszopiclone (Najjar, 2007). Zolpidem may have the highest potential to provoke SRED because it has the highest binding affinity for the target receptor and is most widely used. However other hypnotic (zaleplon)-related SRED has been reported (Molina and Joshi, 2010). Taken together, it could be hypothesized that zolpidem might precipitate SRED by establishing and maintaining the impaired consciousness when partial arousals are triggered by any endogenous and/or exogenous factors. The role of drug formulation has been suggested to mediate the manifestation of zolpidem-related SRED because SREDs in two subjects were related to the use of the controlled-release form (Chiang and Krystal, 2008); however, the drug concentration in the CNS is speculated to be more crucial than the drug formulation per se, because most of the zolpidem-induced SRED in the literatures were derived from the immediate-release form (Table 26.3).

The third component of zolpidem-related SRED is a compulsive behavior in the form of abnormal binge-eating. While the most benzodiazepines could induce hyperphagic response in the mammalian species, zolpidem is relatively neutral to appetite (Soderpalm and Berridge, 2000; Stanhope *et al.,* 1993; Yerbury and Cooper, 1989). The presence of other eating disorders in the case series suggests that the disordered eating behaviors might be released during incomplete arousals caused by both sleep instability and zolpidem (Table 26.3). The association between RLS and zolpidem-related SRED may provide another clue. Presence of dopaminergic dysfunction and clinical response to dopaminergic drugs in SRED have been suggested in previous literatures (Schenck *et al.,* 1991; Schenck *et al.,* 1993; Winkelman, 1998). Additionally, RLS and periodic limb movement during sleep were commonly associated with SRED (Schenck *et al.,* 1991, 1993; Winkelman, 1998). Recent reports from an Italian group has confirmed through video-

polysomnography that there is higher prevalence of periodic movements in limb or dyskinesia (77.1%) and periodic muscle activations in orbicularis oculi and masticator (82.9%) (Vetrugno *et al.,* 2006). The same group also documented much higher prevalence (33%) of SRED in RLS subjects than in the control group (1%) (Provini *et al.,* 2009), and this number is higher than the estimated prevalence of SRED in psychiatric- and non-psychiatric populations (Winkelman *et al.,* 1999). Circadian fluctuation in both RLS and SRED is a well-established phenomenon. Dopamine is involved with the reward mechanism in the mesolimbic circuit. Its dysfunction has been regarded as the key mechanism underlying the RLS or the periodic limb movements (Paulus *et al.,* 2007), and its association with the risk of binge eating has also been noted (Blum *et al.,* 1995). Therefore, it could be speculated that dopaminergic dysfunction might contribute not only to the development of SRED but also to the association between RLS and SRED. However, the association between RLS and nocturnal eating syndrome or other daytime eating disorder is yet to be clarified (Winkelman *et al.,* 1999).

26.5 Zolpidem and sleep-related eating disorder: management

The most effective treatment for zolpidem-related SRED regards the drug withdrawal and treatment of co-existing sleep disorders such as OSA and RLS. The presence of other precipitating factors such as alcohol ingestion, cigarette smoking, and partial sleep deprivation should be investigated and minimized through patient education, and it is necessary to document concomitant medications and try to minimize possible drug interaction. Non-pharmacological treatments for insomnia should be considered if hypnotics could not be withdrawn because of persistent insomnias. The effectiveness of cognitive behavioral therapy for insomnia is well-documented, and it can alleviate insomnia symptoms without the side effects of hypnotics (Morin *et al.,* 2009). The use of alternative medication should be also considered. No report has been made on the role of eszopiclone or recently developed hypnotic (ex. ramelteon) in enhancing SRED, but the possibility of their adverse effects cannot be ruled out until clarified with further studies (Zammit, 2009).

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Foods and nutrients that assist sleep

Summary points

- Over 18% of the population use natural products as a sleep aid.
- Almost 30% of those taking nutritional supplements do so for insomnia or sleep problems.
- Sleep is a dynamic behavior during which specific activity of the brain is orchestrated by elaborate and precise mechanisms.
- Based on several high quality studies, melatonin was effective reducing time to sleep onset and reducing nighttime awakenings.
- Vitamin B12 and thiamine were consumed in higher levels in normal sleepers than in those with insomnia.
- Iron-deficiency anemia is associated with restless leg syndrome and periodic limb movements of sleep.
- One study showed that chamomile compared to placebo did not affect sleep time, time required to fall asleep or number of night time awakenings, however, it had modest benefit on feeling more awake and alert in the day.
- Several well-designed studies support valerian as an effective supplement to improve sleep patterns.
- There is insufficient data to support kiwifruit, St. John's wort, hops, kava, vitamin D, and vitamin A for sleep disorders.
- Randomized controlled trials are needed to definitely support the use of many dietary and herbal supplements for sleep.

27. Nutritional supplements and sleep: an overview

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Abstract

Over 18% of the population use natural products as a sleep aid. Almost 30% of those taking nutritional supplements do so for insomnia or sleep problems. Sleep was once thought to be a state of brain rest and inactivity, however, it is now recognized as a dynamic state of consciousness that is orchestrated by elaborate and precise mechanisms. In this chapter, we overview the nutritional supplements used for sleep disorders and current evidence supporting their use. We survey melatonin, B vitamins, iron, chamomile, valerian, kiwifruit, St. John's wort, hops, kava, vitamin D, and vitamin A. Based on several high quality studies, melatonin was effective reducing time to sleep onset and reducing nighttime awakenings. Vitamin B12 and thiamine (vitamin B1) were consumed in higher levels in normal sleepers than in those with insomnia. Iron-deficiency anemia is associated with restless leg syndrome and periodic limb movements of sleep and iron supplementation ameliorates symptoms. Chamomile did not improve sleep, however, improved daytime wakefulness. Several well-designed studies support valerian as an effective supplement to improve sleep patterns. There is insufficient data to support kiwifruit, St. John's wort, hops, kava, vitamin D, and vitamin A for sleep disorders.

Keywords: nutrients, vitamins, sleep, supplements, diet

Abbreviations

AC	Adenylate cyclase
GC	Cyclic guanosine
PR	Prolonged release
SCN	Suprachiasmatic nucleus

27.1 Introduction

It has been estimated that over 18% of the population use natural products as a sleep aid (Gyllenhaal *et al.,* 2000). Modern research on herbal medicine is still in its infancy, but has increased in recent years. There has been a 50% increase in the medical literature regarding nutritional supplements. Specifically, research on the effects of herbs and supplements on brain and behavior has markedly increased. There have been few attempts to organize and try to better understand the medical and health information available on the use of nutritional supplements to improve sleep patterns.

Traditional mainstream drug development typically uses isolated, single active agents that have been synthesized or separated from plants or biological organisms. The goal was to isolate a single active agent from a plant and test it as an independent 'drug.' The 'complementary and alternative medicine' approach uses the whole natural biological product or extracts derived directly from product. Herbs are essentially whole sections of specific plants. It is more commonly accepted now that plant and their extracts contain numerous potentially active components and the presence of several active compounds in one plant may have a synergistic effect.

Herbal supplements act in the brain and their influence on sleep are primarily through regulation of neuronal receptor function (Paredes *et al.,* 2008). Herbal supplements are known to have a range of therapeutic actions that improve sleep through neurotransmitter and neurohormonal influences. The resultant central nervous system benefits include antidepressant, anti-anxiety, sedative, hypnotic and analgesic effects (Spinella, 2001). Depression, anxiety, and pain syndromes are frequently associated with insomnia and sleep disturbance. Therefore, the beneficial effect of a herb or supplement on mood, anxiety or chronic pain would result in a concomitant improvement of the associated sleep disturbance.

The first section of this chapter is devoted to understanding the basic biological nature of sleep and later sections how nutrients can affect this process. The foods and nutrients we consume have an effect on our behavior and physical health. Our sleep behavior is consequently likely affected by our intake of food and supplements.

Dietary intake has been shown to have a direct effect on our body's internal clock. This internal clock, more formally referred to as circadian rhythm, sets the human brain on a day-night schedule of wakefulness, temperature control, appetite and endocrine control. Eating, and

therefore nutritional, patterns have been shown to affect this biological clock. Additional research studies have reported that specific nutrients and food components, such as glucose, ethanol, caffeine, thiamine and retinoic acid, affect the expression of genes that are responsible for the function of the circadian rhythm in the body (Zadeh and Begum, 2011). Therefore, when and what we consume likely effect our sleep pattern.

27.2 The science of sleep

The concept that sleep is a time of brain inactivity has long been replaced with evidence that the brain is actually very active. Research has shown that sleep is a dynamic behavior during which specific activity of the brain is orchestrated by elaborate and precise mechanisms (Stickgold, 2005).

Sleep evolves during life and changes with maturation and aging. During infancy, 16 to 18 hrs a day of sleep is needed. A more prolonged sleep pattern occurs during the night by six months of age. The sleep time requirement in childhood continues to diminish through preadolescence, to about 8 hrs per night. However, during the active growth and learning phase of adolescence, sleep requirements again increase. Insufficient amount of sleep at this age is often secondary to school schedules with the demand for early awakening. The need for sleep remains relatively constant in adulthood, sleep tends to become more fragmented as we age, and night sleep may decrease with some compensating with daytime napping (Bliwise, 1993).

Sleep occupies approximately one-third of the adult life. Sleep deprivation effects mood, cognitive and motor performance and increases our risk of health problems. Irritability, anxiety, poor motivation and symptoms of depression are frequently seen in those with insufficient sleep. Cognitive problems include poor concentration, slower reaction times, distractibility, forgetfulness and poor coordination. Several studies have shown there is an increased risk of hypertension, coronary artery disease, and obesity as well (Levy *et al.*, 2012).

Sleep-dependent memory encoding and consolidation occur every night during sleep. Although determining how sleep contributes to our memory has been complex, there is clear evidence that memory processing during sleep is an important component of how our memories are formed and ultimately shaped. Memory formation and storage reflect molecular and cellular activity that converts fragmented memory representations into more permanent forms and enables us to recall information over extended periods (Stickgold, 2005). These processes, which are dependent on sleep, allow us to continually collect and integrate information in our memory and permit learning.

Sleep is considered a biological function that affects other biological systems in the body. Several compensatory regulatory mechanisms occur in most mammals after sleep deprivation. These include changes in heart rate, sleep continuity, and reduced arousal threshold, alertness, and motor activity (Levy *et al.,* 2012).

The incidence of insomnia in the general population is approximately 13%. The most common causes of insomnia are late-day napping, caffeine and nicotine intake, exercising in the hours immediately before bed, and late-night meals. Also using the bedroom to work, read, eat, or watch television in the evening before bedtime may interfere with the ability to fall asleep. However, many experience insomnia that are not related to any of these behavioral factors. When the lack of sleep begins to effect daytime function, treatments are sought.

27.3 Sleep and supplements

Herbal and natural products represent one of the most common forms of complementary and alternative medicine. Almost 30% of those taking nutritional supplements do so for insomnia or sleep problems (Meoli *et al.,* 2005). This high number of people taking nutritional supplements for sleep is likely due the problems and side effects associated with prescription medications. The most common side effects are excessive daytime sleepiness, nausea and poor concentration and dizziness during the day. The use of many prescription medications for the treatment of insomnia is accompanied with the concern of becoming addicted.

27.3.1 Melatonin

The pineal gland is an endocrine gland in the brain that synthesizes and secretes melatonin (N-acetyl-5-methoxytryptamine). The input to the pineal gland is transmitted from the retinal preceptors in the eye. The day/night cycle of melatonin secretion is controlled by a vision-processing center in the brain and is strongly influenced by light. The main effect of light is to regulate melatonin secretion in synchrony with the day's light-dark cycles. Light is first detected by melanopsin-containing retinal cells and transmitted to the SCN of the hypothalamus via the retinohypothalamic tract. The superior cervical ganglion delivers the SCN input to the pineal gland (Brzezinski *et al.*, 2005). Melatonin secretion increases abruptly in the evening as sunset begins. As bedtime approaches the melatonin release continues to increase and reaches a peak level between 2 and 4 am. The release of the melatonin gradually falls during the latter part of the night and is present at very low levels during the day (Espana and Scammell, 2004).

Melatonin is a natural hypnotic and has been determined to be a safe and effective sleep aid for long-term use in the elderly (Wade, 2007). Melatonin has minimal toxicity and a limited side effect profile. Melatonin replacement therapy has been found beneficial in treating sleep disturbances. Impaired melatonin secretion has been implicated in various other diseases (Ekmekcioglu, 2006) amongst which:
- coronary heart disease
- non-dipper hypertensives
- cardiac syndrome X
- cancer
- alcoholism

- Alzheimer's type dementia
- primary insomnia
- psychiatric disorders
- sepsis

The melatonin precursor tryptophan is absorbed from the gastrointestinal tract into the blood stream and converted into serotonin (Figure 27.1). Serotonin is acetylated and undergoes enzymatic modification to form melatonin. The pineal gland has the highest concentration of melatonin in the body and secretes low levels of the hormone during the day and increases secretion as daylight diminishes (Arendt and Skene, 2005).

The effect of light on the SCN, and subsequently the pineal gland, regulates the sleep/wake cycle. The SCN firing rate is influenced by melatonin receptors MT1 and MT2. These receptors are metabotropic G-protein coupled receptors. The MT1 and MT2 receptors are abundantly expressed in the SCN (Table 27.1). This system complex acts by the G protein-linked receptor family and is involved in three intracellular processes that ultimately play a role in the regulation of circadian rhythm. The MT1 and MT2 receptors inhibit AC, GC, and phosholipase in the phospholipase C pathway.
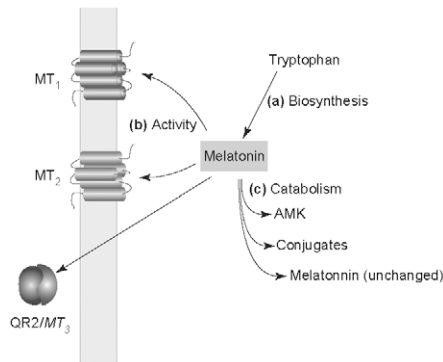
Figure 27.1. Melatonin pathways. (a) Biosynthesis. Melatonin is synthesized from tryptophan. Hydroxylation at position 5 of the indole moiety of tryptophan and decarboxylation leads to the formation of 5-hydroxytryptophan, which undergoes methylation of a hydroxyl group in position 5 and N-acetylation to form melatonin. (b) Activity. Melatonin acts through three known binding sites, MT_1 and MT_2 receptors and the cytosolic enzyme quinone reductase 2 ($QR2/MT_3$), which is involved in toxification and detoxification processes. (c) Catabolism. The catabolism of melatonin is mediated through two main pathways. Sixty percent of melatonin is hydroxylated at position 6 and further conjugated to the hydrophilic moieties glucuronyl or sulfate groups, catalyzed by UDP-glucuronosyltransferase or sulfotransferase, respectively. Furthermore, ~15% is metabolized by myeloperoxidase and/or by indoleamine-2,3-dioxygenase, leading to the pharmacologically active N1-acetyl-5-methoxy-kynurenine (AMK) (a member of the family of kynurenamines). About 25% of melatonin remains unchanged (Boutin *et al.* (2005) with permission from Elsevier Limited).

Table 27.1. Melatonin receptors in the human central nervous system (adapted from Ekmekcioglu, 2006, with permission from Elsevier Limited).

Location	Receptor subtype	Proposed function
Suprachiasmatic nucleus	MT1	modulation of circadian rhythm
		induction of sleep
Various retinal cells	MT1, MT2	inhibition of stimulation evoked release of dopamine
		modulation of rod phototransduction pathways and photoreceptor function
		adaptation to low light intensities
Hippocampus	MT1, MT2	memory, excitation and inhibition of neuronal activity variations in Alzheimer disease
		enhancement of seizure threshold via depression of GABAA-receptor function
Cerebellum	MT1, MT2	interactions with glutamatergic synapses
Central dopaminergic system	MT1	modulation of dopamine synthesis and release
		modulation of dopamine synthesis and release
		modulation of dopamine synthesis and release
Various regions	MT1	unknown
Unknown	MT3	anxiolytic

The result of melatonin binding to MT1 and MT2 receptors in the SCN is to inhibit the AC and GC pathways with net reduction in cellular excitability by inhibiting Ca2+ channels and enhancing K+ channels. The combined effect is the inhibition of the SCN firing. The MT1 receptor has been implicated in the hypnotic effect of melatonin while the MT2 receptor has been implicated in the phase shifting effects of melatonin (Dubocovich *et al.,* 2003). Recently, an additional melatonin-binding site termed MT3 has been identified as a quinone oxidoreductase 2, but its role in sleep and circadian rhythm has not been elucidated (Leclerc *et al.,* 2011).

Exogenous melatonin is used commonly for both hypnotic and circadian entrainment reasons; however, the clinical use of melatonin is complicated by unstandardized commercial preparations, and variability of effect and blood levels between users. Despite the variability in preparation and dose-response dynamics, a meta-analysis suggested that melatonin improved objective sleep measures such as latency, efficiency, and total sleep time, although effects were small and possibly influenced by subjects with delayed circadian phase (Buscemi *et al.,* 2005). Moreover, Brzezinski and colleagues (2005) conducted a meta-analysis of 284 subjects in 17 studies to evaluate the effectiveness on exogenous melatonin. The authors concluded that melatonin was effective reducing time to sleep onset and reducing nighttime awakenings.

Orally administered melatonin is rapidly absorbed, with peak plasma concentrations occurring between 20 and 120 min. Improved sleep onset and quality is seen with 1-3 mg doses. This is effective for those who have trouble falling asleep. However, this is inadequate for those with frequent nighttime or early morning awakening. Therefore, in order to maintain continued elevated concentrations of melatonin throughout the night, repeated administration of low doses is required. Recently, a formulation of a prolonged-release melatonin (PR-melatonin) was made available to provide a sustained elevation of melatonin throughout the night and more closely mimics to the normal physiological release pattern of endogenous melatonin (Wade *et al.,* 2007).

The sleep-promoting effects of melatonin become most prominent about two hours after intake, similar to the physiological sequence at night. It has been demonstrated that melatonin participates in the regulation of the sleep-wake cycle by inhibiting the wakefulness-generating system in the SCN (Shochat *et al.,* 1998). Melatonin was found to be effective in adjusting the sleep-wake cycle in blind individuals, where the light-dark cycles do not exist (Arendt *et al.,* 1997). In addition, exogenous melatonin administration synchronized neuroendocrine rhythms (e.g. cortisol and body temperature) to the day-night cycles in blind subjects as well (Sack *et al.,* 2000). Melatonin enables phase shift of circadian rhythms to induce transient sleepiness and to suppress core body temperature.

Melatonin has a short half-life and therefore is less effective with those who have problems with frequent nighttime awakenings or early morning awakenings. Patients with insomnia were treated with PR-melatonin 2 mg at bedtime for three weeks compared to a control group treated with placebo. In the PR-melatonin group there were improvements in sleep latency and in subjective quality of sleep as well as improved daytime functioning. The subjects taking melatonin were found to have no impairment of vigilance the following day and even some improvements in performance in the morning. The reported quality of sleep, number of nighttime awakenings, morning alertness and quality of life were significantly improved with PR-melatonin compared to placebo (Wade *et al.,* 2007). The sleep-promoting effects of PR-melatonin are similar in magnitude to those of other hypnotics (i.e. zaleplon and zopiclone). At the same time, PR-melatonin does not impair psychomotor performance such as driving performance, and memory.

Melatonin is also found in small amounts in the plants that used in Feverfew (*Tanacetum parthenium*) and St John's wort (*Hypericum perforatum*) (Paredes *et al.,* 2008).

Ramelteon is the first FDA approved medication designed to mimic the effects of melatonin. It similarly acts by activating MT1 and MT2 receptors in the SCN. The advantage of Ramelteon is that it is regulated as a drug and therefore the purity and strength are standardized with specific dose recommendations. The recommended dose is 8 mg, the peak absorption occurs between 30-90 minutes, and the drugs half-life is 1-2.6 hrs.

27.3.2 B vitamins

There are five forms of vitamin B: thiamine (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3), pyridoxine (vitamin B6), and vitamin B12. The B vitamins play an integrate role in the function of neurons both in the brain and throughout the body. This group of vitamins is also involved in many metabolic functions, including protein and glucose synthesis. Deficiencies in B vitamins can occur as a result of poor intestinal absorption, corticosteroids or certain anti-seizure medication use, and impairments in renal and hepatic function.

A large study evaluated the dietary intake in individuals with insomnia and normal sleepers. It found significant differences in the consumption of several B vitamins (Zadeh and Begum, 2011). Both vitamin B12 and thiamine were consumed in higher levels in normal sleepers than in those with insomnia.

Vitamin B12 is reported to affect the body's biological rhythm including the circadian rhythm. Clinically B12 supplementation improves the symptoms of sleep-wake rhythm disorders. Experimental studies on humans and clinical evidence suggest that vitamin B12 plays a role in the entraining mechanism of the biological clock and allows for a more regular sleep pattern.

Thiamine and B12 are key mediators of brain cell function. In addition to maintaining healthy cells in the brain, B12 plays a significant role in the formation of GABA in the brain. Animal studies have shown increased levels of B12 result is a corresponding increase in GABA during sleep (Ikeda *et al.,* 1997).

Nocturnal leg cramps significantly affect sleep in some elderly patients and women during pregnancy. In a randomized, double blind, placebo-controlled study in elderly patients suffering from frequent nocturnal leg muscular cramping showed significant improvement when they were administered vitamin B complex capsules (Chan *et al.,* 1998)

27.3.3 Iron

Iron has not been shown to directly improve sleep parameters, however, iron was found to be consumed more in individuals with normal sleep patterns than those with insomnia (Zadeh and Begum, 2011). In addition, iron-deficiency anemia is readily associated with the restless leg syndrome and in many cases resolved with iron therapy (Allen *et al.,* 2011). In addition, iron has been found to be an etiological cause of periodic limb movements of sleep and responds to administration of supplemental iron therapy (Simakajornboon *et al.,* 2003).

27.3.4 Chamomile (*Chamomilla recutita* or *Matricaria recutita*)

Chamomile has been used for many years for a variety of health conditions. There are two forms: Roman and German. It is most commonly used for insomnia, anxiety and gastrointestinal problems. The flower of the chamomile plant is dried and used for teas, capsules and tablets. A

liquid extract is also available. Chamomile binds to GABA receptors and increases its level in the brain (Awad *et al.,* 2007).

A randomized, placebo-controlled, double blind study evaluated the effectiveness of chamomile for the treatment of insomnia (Zick *et al.,* 2011). Placebo or 270 mg of chamomile was administered to 34 adults with insomnia. The subjects' reports revealed no difference in sleep time, time required to fall asleep, or number of night time awakenings. There was a 'modest' benefit rating for chamomile on the daytime function score – those patients who were administered chamomile reported feeling more awake and alert the following day. There was also reduced time required to fall asleep and there were fewer nighttime awakenings in the chamomile group. There were no differences in side effects between placebo and chamomile.

27.3.5 Valerian (*Valeriana officinalis*)

Valerian is a plant originally found only in Europe and Asia but is now cultivated in North America. The dietary supplement is derived from the roots and the stems of the plant. These components are dried and prepared for teas and tinctures. The extracts of the valerian plant that are incorporated into capsules and tablets include many different components. There are two types of oils in the plant as well as a substance comprised of iridoids. It is believed that the combination of two oils in the valerian plants, sesquiterpenes and valepotriates, are responsible for the beneficial sleep effects (Hendriks *et al.,* 1981). Both of these oils have been shown to have sedating effects in animals. Valerian increases both GABA and serotonin levels (Holz and Godau, 1989).

There have been nine clinical trials of the effects of valerian as a treatment for insomnia. Three were designed with the highest clinical protocols to determine the effectiveness without bias and are reviewed below.

The first study looked at 128 individuals without a diagnosis of insomnia and was designed to evaluate time to fall asleep, quality of sleep, and number of nighttime awakenings (Leathwood *et al.,* 1982). Although these are all subjective ratings, the participant was randomized to either placebo or the valerian preparation and therefore did not have a bias when reporting their scores. There were statistically significant findings that supported the administration 400 mg of valerian aqueous extract in all endpoints.

The second study included only eight subjects with difficulty falling asleep and were randomly assigned to placebo, or 450 mg or 900 mg of aqueous valerian (Leathwood and Chauffard, 1985). The subjects wore nighttime motion recorders on their wrist and onset of sleep was determined as the first five-minute period without movement. The time to sleep onset was seven minutes sooner in the valerian 450 mg group, however, with only eight subjects in this study, this was not considered a clinically significant difference from placebo. Incidentally, the valerian 900 mg resulted in more subjects reporting sleepiness in the following morning.

The third study randomized 121 subjects with a diagnosis of insomnia to either placebo or 600 mg of dried valerian root for 28 days (Donath *et al.*, 2000). The group receiving the valerian extract showed a decrease in insomnia on several clinical assessments compared with the placebo group.

In summary there have been several well-designed studies that support valerian as an effective supplement to improve sleep patterns. 400 and 450 mg of the valerian aqueous solution and 600 mg of the dried root preparation were effective.

27.3.6 Kiwifruit (*Actinidiaceae*)

There have been several studies that have assessed the effect of kiwifruit on sleep. Kiwifruits are native to eastern Asia and their use for treating several medical conditions has been reported. It is high in serotonin, antioxidants, flavonoids, anthocyanins, and vitamins C and E.

In one study, 22 subjects were asked to eat two kiwis one hour before going to bed for four weeks (Hsiao-Han *et al.*, 2011). The patients maintained a sleep diary and completed a questionnaire. In addition, they wore a nighttime motion recorder each night to assess sleep onset and duration. There were significant increases in total sleep time and sleep efficiency measured by the sleep/activity monitor during the nights kiwi was consumed. The major limitation of this study is that it was an open label. Nonetheless, the findings are important and do suggest kiwi fruit may help promote a good sleep pattern.

27.3.7 St. John's wort (*Hypericum perforatum*)

St. John's wort enhances serotonin activity and inhibits glutamate activity in the brain. It has been shown in many studies to have beneficial effects on anxiety and depression (see Butterweck, 2003 for a review). However, there are no studies showing that St. Johns wort improves sleep in those without depression. Moreover, sleep studies with polysomnograms have revealed no effect on sleep architecture in those taking St. Johns wort (Sharpley *et al.*, 1998).

27.3.8 Hops (*Humulus lupulus*)

Hops work on the melatonin system. It has been shown to have the ability to bind to melatonin receptors and simulate its effects (Butterweck, 2007).

A study designed to examine the interaction of sedative herbs with selected central nervous system receptors revealed that a hop dried extract was found to bind to serotoninergic 5-HT6 receptors as well as melatoninergic ML1 receptors (Abourashed *et al.*, 2004). The involvement of 5-HT receptors in depression and sleep disturbances has been demonstrated and the role of melatonin in the regulation of circadian rhythm is well established. Ultimately, no study has shown improvement in sleep pattern with hops.

27.3.9 Kava (*Piper methysticum*)

Kava is used to treat anxiety and sleep disorders in Europe and the US. It exerts its effects as a central nervous system depressant. Animal studies confirmed that it acts on GABA binding in neurons (Schultz *et al.,* 1998). A well-designed study revealed the biological activity on GABA receptors was similar to benzodiazepines (Woelk *et al.,* 1993).

There have been several studies indicating kava is effective in treating anxiety, but few convincing studies on sleep in subjects without anxiety traits (Klimke and Has, 1992; Volz and Kieser, 1997). There have been no cognitive side effects noted on formal testing with doses as high as 600 mg.

27.3.10 Vitamin D

Vitamin D has recently been implicated in numerous bodily functions and preventative disease strategies. Chapter 24 by McCarty and Marino in this book discusses vitamin D deficiency and sleep in detail. Furthermore, a compelling study from Saudi Arabia evaluated the treatment of fibromyalgia and associated sleep symptoms (Matthana, 2011). The authors found that 42 of 61 women with fibromyalgia and vitamin D deficiency had marked reduction in their symptoms including problems with sleep. It is not clear whether vitamin D simply reduced the painful symptoms of fibromyalgia so the women slept better or if vitamin D treats the core of the sleep problem in individuals with fibromyalgia. Regardless, there is still no evidence vitamin D effects sleep in healthy persons..

27.3.11 Vitamin A

Nuclear retinoid receptor proteins are highly dependent on vitamin A to maintain function and structure. There is experimental data that illustrates vitamin A metabolites retinoid play a critical role in the signaling mechanism of the homeostatic component of sleep regulation (Hiroyoshi, 2008). Maret and colleagues (2005) demonstrated that gene encoding of the retinoic acid receptor determines the contribution of delta oscillations to the sleep electroencephalogram. The authors concluded that retinoic acid signaling regulates cortical synchrony in the adult sleep patterns. No clinical data exists on the use of vitamin A for sleep.

27.4 Conclusion

Several foods and nutrients have traditionally been associated with sleep status. Researchers have recently begun to investigate the effectiveness of such foods as substitutes for pharmacological interventions. The effects of food and food constituents on sleep disturbances are only beginning to be understood. It is noteworthy to mention that sleep-related problems are associated with specific food consumption behaviors including tea, coffee, or alcohol, as well as, eating protein and fat rich food just before bedtime.

There are many well-designed research studies that have demonstrated associations between food and nutrient deficiencies and sleep disturbances. However, similar research is still needed to firmly establish the effectiveness of nutritional supplements in management of insomnia. The studies presented in this chapter certainly support the fact that many nutritional supplements and herbs are beneficial in treating some sleep disturbances, but the field of herbal and nutritional science is still very young.

The available literature provides basic evidence that certain nutrients and herbs positively affect sleep by altering neural responses and re-establishing NREM (non-rapid eye movement) and REM (rapid eye movement) sleep patterns. The precise role of specific nutritional supplements, or combinations of them, will be the subject of future research. Meanwhile it appears clear that several of the supplements, such as melatonin, valerian, and chamomile have sufficient support that they are effective in promoting an improved sleep pattern. It is likely the addition of other supplements may have a synergistic effect. Equally important regarding the current use of any of the supplements reviewed in chapter is that they appear relatively safe.

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Summary points

- Breast milk is the optimal food for babies and its composition varies dynamically during the day.
- Breast milk contains elements whose concentrations follow a circadian rhythm. In this way some elements are present during daylight hours and other ones are present during dark hours to regulate infants' sleep/wakefulness circadian rhythm. These elements include nucleotides, amino acids, hormones, neurotransmitters or even their own precursors.
- In recent years there has been a tendency to make formula milk as similar as possible to breast milk.
- Our research group has demonstrated that the administration of formula milk dissociated into its day/night components helps to consolidate sleep/wake rhythm in babies. On the other hand some plant extracts are added to increase the sedative effect of formula milk and, in this way, improve sleep in infants.

28. Components in formula milks that improve sleep

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Abstract

Human milk is the nonpareil food for the first six months of life. Breast milk is a non-static biological fluid and so it is a dynamic fluid that changes not only over the course of the period of lactation but also during the day. As a result, the design of formula milk has to be as similar as possible to breast milk because this contains nutrients for sleep and for awakening according to the time of day. For several years already, some manufacturers of formula milks have been trying to improve sleep in babies who suffer from sleep problems by adding substances that promote sleep, for instance the essential amino acid tryptophan or vegetable extracts like chamomile or valerian among others. Other vegetable extracts have also been proposed, which are reported to be able to enhance sleep in children. Therefore, by applying chrononutrition – a field of chronobiology that establishes the principle of consuming foodstuffs at times of the day when they are most useful for health – to infant formula milks, we can increase sleep in babies.

Keywords: chrononutrition, infant formula milk, sleep

Abbreviations

CNS	Central nervous system
GABA	Gamma-amino butyric acid
MCT	Medium-chain triglyceride

28.1 Introduction to breast milk: the perfect food

Human milk is the best, and indeed unequalled, food for infants. It provides all the nutritional components needed during the first months of life. Because of its composition, it is an essential component of nutrition up to two years, supplemented by other non-dairy foods. The composition of this fluid varies dynamically both in accordance with the infant's requirements over time (with variations in composition and volume over the course of the period of lactation) and during the day. In particular, many of its nutritional components which intervene in the sleep/wake cycle present circadian oscillations (Sánchez *et al.*, 2011).

All this is grounded in the fact that, at the time of birth, the infant becomes separated from its mother's endogenous biological rhythms. With this loss of the maternal biological clock, it has to adapt to the external environment. For this reason, some of the components of breast milk involved in sleep present circadian oscillations which contribute to the consolidation of the infant's own circadian rhythms (Madrid and Rol de Lama, 2006).

In this chapter, we will focus on the circadian oscillations of certain of these components of breast milk in order to gain insight into how to approach the development of artificial milk formulas that are capable of reproducing as effectively as possible the composition of breast milk. In this way, we will be able to help regulate the sleep/wakefulness rhythm using artificial formulas during the first months of life of infants who cannot be fed with breast milk.

28.2 Nutritional elements present in breast milk that are involved in the sleep/wake rhythm

Various studies over the last two decades have reported observing circadian fluctuations of certain nutritional elements in breast milk. This is the case for the minerals calcium and magnesium, and the trace elements iron, zinc, and copper (Karra and Kirksey, 1988; Picciano and Guthrie, 1976). Moreover, melatonin, which is principally responsible for regulating circadian rhythms, presents circadian variations in breast milk, with its acrophase (the time of maximum concentration) being during the night (Engler *et al.*, 2011; Illnerová *et al.*, 1993). Some amino acids, including tryptophan (precursor of serotonin and melatonin), also have a circadian rhythm with acrophases during the period of darkness.

28.2.1 Nucleotides

Nucleotides are molecules that participate in cellular signalling and are present in breast milk. It has been reported there is an increase in nucleotide concentration in the mature milk (from day 15 *postpartum*) relative to the calostrum (4-5 days *postpartum*). A review of the literature has revealed that three nucleotides are involved in sleep: uridine-5´-monophosphate, adenosine-5´-monophosphate and guanosine-5´-monophosphate. Chronobiological research has shown that adenosine-5´-monophosphate and guanosine-5´-monophosphate, cytosine-5-monophosphate and inosine-5´-monophosphate have a circadian rhythm (Cubero *et al.,* 2009; Sánchez *et al.,* 2009).

28.2.2 Amino acids

Recent studies have shown that, as the milk matures, rhythmic nutritional components are added. Tryptophan, alone among the amino acids, follows a circadian rhythm from the colostral stage. The amino acid methionine is incorporated in the transitional milk stage, and subsequently in the mature milk the amino acids tyrosine, histidine, phenylalanine, and aspartate are added to the rhythmicity.

Tryptophan is an essential amino acid in infant nutrition. It is a precursor of the neurotransmitter serotonin and of the hormone melatonin. This amino acid is the first to acquire a circadian rhythm; in fact, it is the only amino acid which shows a circadian rhythm from the colostral stage in breast milk (Figure 28.1). It is wellknown that tryptophan oral administration modifies the circulating levels of serotonin and melatonin which are key substances in the regulation and quality of sleep.
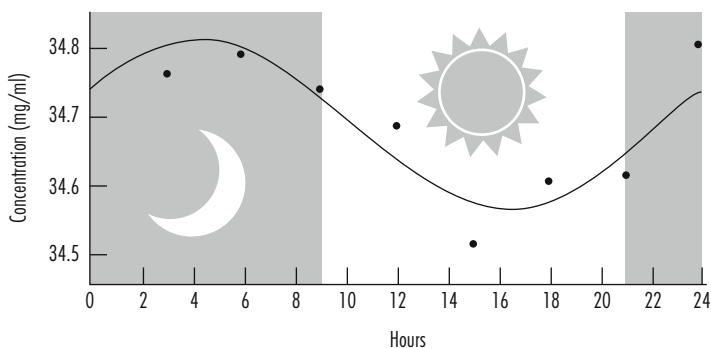
Figure 28.1. Tryptophan rhythm in the colostral stage. Sinusoidal function obtained by cosinor of the amino acid tryptophan in colostral milk.

The amino acid methionine shows a circadian rhythm from the transitional stage. This amino acid is a precursor of the neurotransmitter acetylcholine which is responsible for controlling and maintaining wakefulness through the ventrolateral pre-optic area of the hypothalamus and controlling the REM sleep in the nucleus reticularis pontinus oralis. Experiments with quails showed that oral administration of L-methionine increased diurnal activity. This result would explain the rhythmicity of L-methionine in breast milk (Sánchez *et al.,* 2010).

Finally, it is in the mature stage that the circadian rhythms of the activity-promoting neuroactive amino acids are established: phenylalanine, and essential amino acid and, together with tyrosine precursor of epinephrine and norepinephrine, methionine, and essential amino acid and precursor of acetylcholine, and aspartic acid and glycine, activity neurotransmitters and therefore with their acrophase during wakefulness. As regards histidine – an activity neurotransmitter – its acrophase is contradictory since it occurs during the period of darkness: a possible explanation would be that it is a semi-essential amino acid at this stage of life, so its endogenous levels may not be influenced by its intake with food.

28.2.3 Neurotransmitters and hormones

Serotonin is synthesised from the amino acid tryptophan and released in the raphe nuclei (Cubero *et al.,* 2011; Sánchez *et al.,* 2008). It is a metabolite that affects sleep, specifically sleep latency. Our group has been able to confirm its presence in human milk, although no circadian variations of this neurotransmitter have as yet been described.

On the other hand, melatonin, which is synthesised from serotonin, also participates in sleep regulation (Figure 28.2). Melatonin is more involved in sleep quality than in sleep onset. This indole is mainly produced during dark hours by the pineal gland from serotonin. Specialised photoreceptive cells in the retina detect lack of light and this information goes directly to the suprachiasmatic nuclei through the retinohypothalamic tract and indirectly through the geniculohypothalamic tract. N-acetyltransferase, which constitutes the limiting step in melatonin synthesis in the pineal gland, produces the indole only during darkness. Studies have reported that sleep/wake circadian rhythm disruption due to ageing is related to a decline in melatonin levels, causing negative effects on health and mood.

It is well documented that melatonin exhibits circadian rhythm in plasma, saliva and human milk among others biological fluids (Almeida *et al.,* 2011; Engler *et al.,* 2011). In the breast milk melatonin shows high levels during dark hours and there is a decrease during the day. In this way, lactating mothers communicate time of day information to their babies and coordinate them with *zeitgebers*. In this way the mother prepares the baby for sleep through her breast milk.

The objective of these variations in breast milk is to regulate the infant's circadian rhythms, including the sleep/wakefulness cycle. Thus the wake-promoting substances occur during the day, and the sleep promoters during the night.
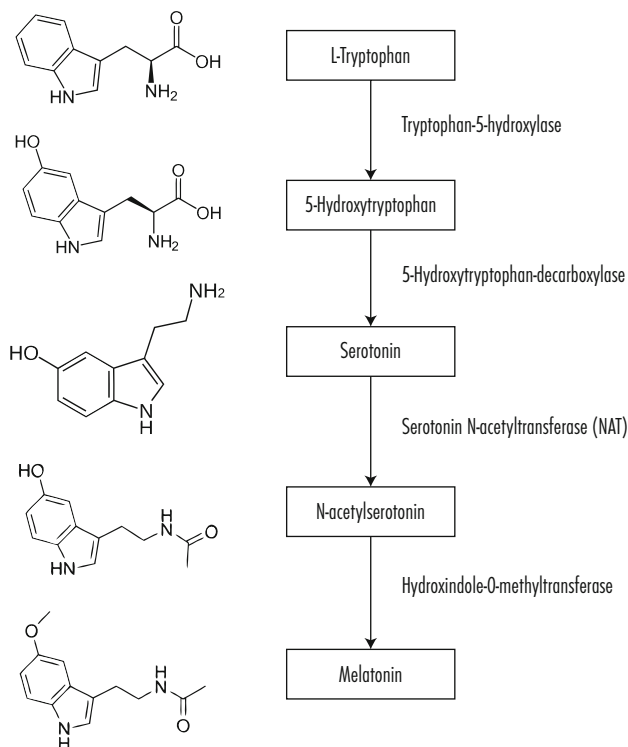
Figure 28.2. Melatonin synthesis pathway. Essential amino acid tryptophan which is metabolised to serotonin due to tryptophan hydroxylase – the rate limiting step in serotonin synthesis – and L-aromatic amino acid decarboxylase. In the pineal gland, during dark hours, serotonin is further metabolised to melatonin thanks to serotonin N-acetyltransferase – activated only during dark hours – and o-methyltransferase.

28.3 Articifial milks that influence infant's sleep/wake behaviour

Infant food manufacturers have made efforts to design milk formulas that approximate breast milk as closely as possible. Nevertheless, complete equality is impossible due, amongst other things, to the fact that proteins or cellular elements of the milk of each animal species are essentially different. In addition there are documented differences in relatively simple components such as the high uridine and tryptophan content of breast milk which, until now, has not been reflected in commercial infant milk formulas. Indeed, the tryptophan concentration of breast milk is 2.5% of the total proteins, whereas in most commercial formulas the corresponding measured tryptophan content is 1.5%.

There are marked circadian variations in the composition of human milk that must have a key functional importance in the development of pre-weaning infants. Nevertheless, until now no infant food formulas have been developed to take these aspects into consideration, although the information on the circadian variability of milk has been known for decades. For example, several

studies have demonstrated that the acrophase and nadir of the circadian variability depend on the component in question: the amino acid tryptophan reaches maximum levels in breast milk during the night, while the maximum values for the sleep-inducing peptide, sodium, potassium, and cortisol, and folates and lipids are reached at dusk (Cubero *et al.,* 2007).

Given these facts, and the involvement of the components present in breast milk in the development of the sleep/wake rhythm, dissociated day/night formula milks for pre-weaning infants were designed to take account of the function of the substances that intervene in the infant's sleep/wake behaviour. These formulas were designed by Ordesa Laboratories S.L. University of Extremadura and University of Islas Baleares. Nutritional components for infant formula milks were dissociated into two separate preparations according to whether their nutritional components facilitated sleep or wakefulness. To this end, the night milk contained the sleep neuromodulating nucleotides uracil and adenine, MCTs that because of their easy digestion facilitate sleep in pre-weaning infants; high levels of tryptophan and of carbohydrates to raise circulating insulin levels and facilitate transport through the blood-brain barrier; and low levels of proteins in order to reduce the competition of tryptophan with other neutral amino acids both in intestinal absorption and passage through the blood-brain barrier. MCTs, which are better absorbed than long-chain triglyceride, also improve fat and nitrogen absorption; therefore, MCTs can increase tryptophan absorption and its availability to produce serotonin and melatonin. In addition, MCTs increase cholecystokinin levels, which promotes sleep although its mode of action is still poorly understood (Telliez *et al.,* 1998).

28.4 Nutritional components in artificial milks that improve sleep

Sleep studies in infants with more than 3 nocturnal awakenings have shown that infant milk formulas adapted to the chronobiology of human milk – Blemil Plus Día and Blemil Plus Noche marketed by ORDESA, S.L. – lead to improved consolidation of the circadian sleep/wake cycle in artificially fed infants. This represents an advance in the field of chrononutrition because the choice of the food ingested during the day or night can contribute to correcting the natural functioning of the circadian system.

The following paragraphs will briefly describe other nutritional elements that may promote sleep (Cubero *et al*., 2011; Murgia *et al.,* 2008). Some of them have already been incorporated into baby foods with this purpose in mind.

28.4.1 Chamomile – *Matricaria recutita* (Asteraceae)

It has now long been demonstrated that chamomile has sedative properties which can be beneficial for infant colic or diarrhœa. This action is due to its content of flavonoids and essential oils which have an affinity for GABA receptors, and benzodiazepines. The result is an inhibition of the CNS. In the adult, the recommended dose is age-dependent and proportional to the weight (adult: 50-300 mg of dry extract 3 times daily).

Nestlé markets cereals enriched with chamomile (Cereal Infantil Nestlé Nestum Plus Arroz y Manzanilla®) to promote a more restful sleep.

28.4.2 Hops – *Humulus lupulus* (Cannabaceae)

Hop inflorescences yield a resinous extract that is rich in alpha and beta acids, polyphenols, and essential oils that give beers their healthy properties. One of these substances is the alpha acid 2-methyl-3-buten-2-ol which raises the levels of GABA, and thus inhibits the CNS. Another is myrcenol which, being a positive modulator of GABA receptors, also has a sedative effect. No effects have as yet been described in very young children.

28.4.3 Lemon balm – *Melissa officinalis* (Lamiaceae)

The leaf extract of this plant is characterised by its affinity to cholinergic receptors, with an action primarily on the limbic system. This is due to its choline content which is of the order of 10^{-8}-10^{-6} M. The plant thus has soothing and sedative properties, in particular against gastrointestinal irritation, among others. At recommended doses, there are no contraindications except for isolated idiosyncratic cases. The toxicologically is safe.

Artificial formulas developed by Nutribén Laboratories include cereals enriched with extracts of lemon balm and linden (see below) to improve the sleep of newborn and older infants.

28.4.4 Passionflower – *Passiflora incarnata* (Passifloraceae)

The passionflower has been studied because components of its extracts are capable of binding to GABA A receptors. Experiments have shown that it can increase the duration of sleep, and that it has sedative and anxiolytic properties and can even reduce the heart rate.

28.4.5 California poppy – *Eschscholzia californica* (Papaveraceae)

This ornamental plant presents some alkaloids which are agonists of 5-HT1A receptors. They act as smooth muscle relaxants as well as showing vasorelaxant properties. Their effect is also involved in dopamine metabolism by inhibiting the formation of noradrenaline, degrading and inhibiting the synthesis of the enzyme dopamine beta-hydroxylase. Because of these properties, the plant can be used as an anxiolytic, sedative, or hypnotic. The recommended adult dose is 2 g of extract per day. No dose has been described for children.

28.4.6 Common valerian – *Valeriana officinalis* (Valerianaceae)

Valerian is today the species with the best documented clinical efficacy. Its composition may vary with the variety or environmental conditions, but essentially it contains large amounts of GABA, glutamine, and arginine. It also enhances the action of GABA by inhibiting its re-uptake and degradation. It presents muscle-relaxant, sedative, anxiolytic, and CNS depressant properties.

The recommended adult dose is 1-3 g of extract. In children, the dose should be proportional to height or weight, and monitored by the pædiatrician.

28.4.7 Linden – *Tilia cordata* and *T. platyphyllos* (Tiliaceae)

The flowers and bracts of these trees – *T. cordata* (small-leaf linden) and *T. platyphyllos* (large-leaf linden) – present anxiolytic and sedative effects (as well as a proven hepatoprotective effect) because of their content of flavonoids, tannins, and mucilage substances whose molecular structure is very similar to that of the benzodiazepines.

There is currently on the market a formula developed by Nestlé Laboratories which consists of cereals enriched with linden extract to improve sleep in children.

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Summary points

- The indoleamine melatonin, its precursor tryptophan, and the intermediate product between both molecules, serotonin, are present in Jerte Valley cherries. These fruits also possess anthocyanins pigments and phenolic compounds with antioxidant activity.
- The intake of Jerte Valley cherries produce beneficial effects on actual sleep time, total nocturnal activity, assumed sleep, and immobility in humans as well as increasing significantly 6-sulfatoxymelatonin (aMT6s) levels and total antioxidant capacity in urine.
- Similarly, the intake of a nutraceutical product made with Jerte Valley cherries produces positive effects on sleep parameters, and increases urinary aMT6s and antioxidant status in young, middle-aged, and elderly human subjects.
- In young and old rats (nocturnal animals), the intake of the Jerte Valley cherry nutraceutical decreased diurnal activity, whereas nocturnal activity increased. The opposite effect was observed for ringdoves, which are animals with diurnal habits.
- The treatment with Jerte Valley cherries increases the circulating levels of melatonin in both species and restores the amplitude of the activity rhythm in the old animals to that of the non-treated young groups.
- These findings suggest that the intake of Jerte Valley cherries, either fresh or as a nutraceutical product, exerts positive effect on sleep and may be seen as a potential nutraceutical tool to counteract oxidation.

29. Cherry-enriched diets improve sleep from young to elderly populations

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Abstract

During the last years, a number of publications have reported the benefits of consuming cherries. Sweet and tart cherries contain anthocyanins and polyphenols that possess many biological activities, including antioxidant, anticarcinogenic and anti-inflammatory properties. The intake of these fruits has been shown to restore the muscular function, decrease oxidative stress and lipid peroxidation, reduce the expression of pro-inflammatory molecules as well as aid in diminishing the risk to develop diabetes or heart disease. The discovery of melatonin, a potent free radical scavenger and antioxidant, and its related compounds, tryptophan and serotonin, in cherries has added new potential nutraceutical properties to these fruits. Since these bioactive molecules are involved in sleep regulation, research has been conducted to evaluate whether supplementing the diet with cherry fruits exerts positive effects on sleep-wake or activity-rest circadian rhythms. Recent reports point to that. In fact, the intake of Jerte Valley cherries, either fresh or as a nutraceutical product, produces beneficial effects on sleep parameters in humans, including actual sleep time, total nocturnal activity, assumed sleep, and immobility. Similar results have been found in rats and ringdoves, animals that exhibit nocturnal and diurnal chronotypes, respectively. Also, significant increases in 6-sulfatoxymelatonin, a metabolite closely correlated with peak plasma melatonin levels measured during the previous night, and total antioxidant capacity in serum and urine have been observed after consuming diets enriched with cherries. Taken together, these findings suggest a potential health benefit of Jerte Valley cherries on sleep and activity-rest rhythms. This may be especially important in aged populations where endogenous melatonin production has been shown to wane. The incorporation of this metabolite, its precursor tryptophan, and serotonin through Jerte cherry-enriched diets may be seen as a potential nutraceutical tool to counteract age-related sleep disorders and oxidation.

Keywords: melatonin, serotonin, 6-sulfatoxymelatonin, tryptophan

Abbreviations

aMT6s	6-sulfatoxymelatonin
NREM	Non-rapid eye movement
REM	Rapid eye movement

29.1 Introduction

During the last years, a number of publications have reported the benefits of consuming cherries. Research has demonstrated several relevant biological activities that are enhanced or inhibited by constitutive components of cherries suggesting that this fruit holds potential for the prevention of cancer, cardiovascular disease, diabetes, and other inflammatory disorders (McCune *et al.,* 2011). These health-promoting properties have been linked to their content in fiber, potassium, vitamin A, vitamin C, carotenoids, and phenolic compounds including anthocyanins, quercetin, and hydroxycinnamates, among other bioactive molecules. The nutritional and functional characterization of sweet and tart cherries has also uncovered the presence of melatonin in these fruits (Burkhardt *et al.,* 2001; González-Gómez *et al.,* 2009). Melatonin is a tryptophan derivative found throughout the animal kingdom from unicellular organisms to humans. This indoleamine is also present in plants (Paredes *et al.,* 2009). Melatonin functions in all parts of all cells and improves physiological infrastructure. As a result, it enhances cell function and optimizes the ability of cells to survive in hostile environments as well as help them cope with the oxidative disaster that characterizes many disorders and diseases (Paredes and Reiter, 2010). Particularly, this indoleamine has receptor-mediated actions which contribute to its capability in eradicating radicals and reducing oxidative stress. Thus, melatonin stimulates a number of antioxidative enzymes which metabolise reactive products to innocuous agents. The enzymes whose activities have been shown to be upregulated by melatonin include both Cu/Zn and Mn superoxide dismutase, glutathione peroxidase and glutathione reductase. Signaling effects of melatonin also include the down-regulation of prooxidant enzymes, including nitric oxide synthase and lipoxygenase. Among the actions that melatonin may carry out in plant tissues, its role as an antioxidant or growth promoter is most strongly supported by the experimental evidence. Other suggested functional implications include the coordination of photoperiodic responses and regulation of plant reproductive physiology, defence of plant cells against apoptosis induced by harsh environmental conditions, its participation as a free radical scavenging agent and/or upregulator of certain protective enzymes in the senescent process (Paredes *et al.,* 2009).

Pineal melatonin production as well as its levels in the blood are unwaveringly higher at night than during the day in all vertebrates regardless of their daily patterns of activity, that is, diurnal, nocturnal, or crepuscular (Reiter *et al.,* 2009a). Using the fluctuating endogenous melatonin signals, vertebrates synchronize both their circadian rhythms and their circannual reproductive activities (Reiter *et al.,* 2009b). Endogenous melatonin production wanes with increasing age leading some to speculate that its loss contributes to the aging process. This supposition was also based on the numerous beneficial effects that supplemental melatonin displays in terms of

seemingly forestalling some signs of age-related deterioration, including sleep disorders (Reiter *et al.,* 2008). Since melatonin is contained in plants, research has been conducted to evaluate whether supplementing the diet with vegetables rich in the indoleamine exerts positive effects on health (Nagata *et al.,* 2005; Reiter *et al.,* 2005). This is the case of Jerte Valley cherries in relation to sleep (Delgado *et al.,* 2011, 2012; Garrido *et al.,* 2009, 2010). These fruits also contain tryptophan and serotonin, bioactive molecules that, together with melatonin, are involved in sleep regulation (Cubero *et al.,* 2010; González-Gómez *et al.,* 2009), as well as anthocyanins pigments and phenolic compounds with antioxidant activity (González-Gómez *et al.,* 2010). For this reason, it has been hypothesized that Jerte Valley cherry-enriched diets may contribute to the amelioration of sleep and to counteract oxidative damage.

Here, we discuss several important issues related to the sleep-improving and antioxidant actions of Jerte Valley cherries. A concise summary of the investigations that have been performed by our research group in relation to the beneficial effects of consuming these fruits are presented.

29.2 Jerte Valley cherries as a source of bioactive compounds involved in sleep regulation

The health-promoting effects of plant foods and plant-derived beverages have been traditionally attributed to some chemical constituents present in various plant tissues, the most bioactive plant substances being mainly secondary metabolites and natural antioxidants such as isoprenoids, phenylpropanoids and indoleamines, among others (González-Gómez *et al.,* 2010). The cherry fruit is considered a nutrient dense food with a relative low caloric content and a significant amount of important bioactive ingredients, being phenolic compounds the widest group (McCune *et al.,* 2011). These compounds are concentrated in the skin and contribute to sensory and organoleptic qualities of cherries, such as taste and astringency. However, those phenolic compounds not only contribute to these qualities, but also they are bioactive compounds with powerful antioxidant and anti-inflammatory properties (Wang *et al.,* 1999). Moreover, the indole melatonin, which is considered the chemical expression of darkness in animals, has been detected and quantified in Montmorency and Balaton tart cherries and Jerte Valley sweet cherries (Burkhardt *et al.,* 2001; González-Gómez *et al.,* 2009). Apart from its well-known sleep-promoting effects, melatonin has been reported to possess antioxidant, anti-inflamatory and anti-oncogenic properties, which may contribute to the beneficial effects found upon cherry consumption.

The Jerte Valley area (7,500 ha) is located in upper Extremadura (southwestern Spain). It consists of a deep and narrow valley where cherries are cultivated mainly on terraces at different altitudes between 700 and 1,200 meters. The combination of different cultivars planted at different elevations results in a large harvest window. A significant percentage of sweet cherries grown in this area belong to a group of late maturing cultivars collectively called 'Picotas' (unstalked cherries). They include 'Ambrunés', 'Pico Limón', 'Pico Negro' and 'Pico Colorado' cultivars that are harvested until mid July. Those cultivars represent one of the latest ripening sweet cherry cultivated worldwide. Stalked cherries include Bourlat, Navalinda, and Van cultivars. An important characteristic of

Jerte Valley sweet cherries is the taste that combines high sugar content with a slight acidity and a firm pulp (González-Gómez *et al.,* 2009). Some of the autochthonous cherry cultivars grown in this area are considered as POD (protected designation of origin) sweet cherries.

Jerte Valley cherries contain substantial amounts of anthocyanins and polyphenolics. In particular, a total of five different anthocyanin (cyanidin-3O-rutinoside, cyanidin-3O-glucoside, peonidin-3O-rutinoside and aglycones malvidin and cyanidin) and five phenolic compounds (p-coumaroylquinic acid, chlorogenic acid and neochlorogenic acid -flavonoids derivates-, as well as epicatechin and quercetin-3O-rutinoside -flavonol derivates-) have been identified and quantified after subjecting cherry samples to high-performance liquid chromatography (González-Gómez *et al.,* 2010). Moreover, significant correlations between antioxidant activity and p-coumaroylquinic acid and epicatechin have been found. This finding has particular relevance, because epicatechin and other catechin derivates are strongly related to tumor suppression processes. Also, the daily consumption of Jerte Valley cherries could preserve the immune function among other positive effects.

All afore-mentioned metabolites have the shikimate as primary precursor in the biosynthetic metabolic route. Tryptophan, which is also generated directly from shikimate, has been also detected and quantified in Jerte Valley cherries using high-performance liquid chromatography-fluorescence techniques (Cubero *et al.,* 2010). The effects of tryptophan on sleep have been investigated for over five decades and tryptophan supplementation has proven to be effective in sleep disorders. The first study to assess the effects of tryptophan on sleep reported that 5-10 g of tryptophan decreased the time before onset of REM sleep in healthy subjects (Oswald *et al.,* 1996). Since then, much research has been conducted in both healthy and populations with sleep disturbances to explore the effects of the amino acid on sleep parameters. Thus, tryptophan supplementation has been reported to increase electroencephalogram delta potential and the amount of sleep NREM (Ouichou and Pévet, 1992). Moreover, elevations in serotonin and melatonin circulating levels after tryptophan treatment have been closely related with improvements in nocturnal rest (Mateos *et al.,* 2009; Paredes *et al.,* 2007).

The high levels of tryptophan contained in cherries may function in the plant's anabolism as a precursor of the indolamines serotonin and melatonin, which provide marked resistance to environmental stress. Accordingly, the presence of serotonin and melatonin in Jerte Valley cherries has been also reported by using high-performance liquid chromatography with mass spectrometry detection (González-Gómez *et al.,* 2009). However, no correlations between melatonin and serotonin levels in relation to harvesting time have been found for any sweet cherry cultivar assayed. Thus, the different amounts of melatonin and serotonin obtained should be a cultivar characteristic. For example 'Bourlat' cherries were found to contain double amount of melatonin than serotonin. 'Ambrunés' was the cultivar with the highest serotonin levels and melatonin was not detected. Ripening stage also seems to influence the melatonin content of Jerte Valley cherries. Maximum levels of the indoleamine occur at the ripest stages while no quantifiable or very low amounts of melatonin are found for the other ripening stages (González-Gómez *et al.,* 2009). As for serotonin, the correlation between the neurotransmitter content and fruit ripening stage is not so clear.

Both melatonin and serotonin exert important physiological effects in terms of regulation of sleep-wake cycles. In fact, it is generally assumed that the indole melatonin promotes sleep by inhibiting the circadian wakefulness generating mechanism, this effect being presumably mediated by melatonin receptor MT_1 at the central nervous system level (Hunt *et al.,* 2001). Likewise, melatonin reduces sleep latency, improves the maintenance of sleep and slightly modifies its architecture (Barriga *et al.,* 2001), which is crucial in elderly populations since the predominantly nocturnal synthesis of melatonin substantially wanes with advanced age and the onset and progression of age-related diseases. Regarding serotonin, it has been shown that a decrease in daytime levels of serotonin, as a result of low intake of tryptophan during the day, causes sleep disturbances (Arnulf *et al.,* 2002). Moreover, the neurotransmitter serotonin also plays an important role in the regulation of endogenous circadian clock. For instance, serotonin raises the proportion of slow wave sleep (Jouvet, 1999), though it also acts as a wakefulness neurotransmitter. Additionally, blocking the synthesis of serotonin by different mechanisms causes a prolonged insomnia period likely due to diminishing melatonin circulating levels (Gutierrez *et al.,* 2003). In contrast with traditional medicine, which consists in sleeping pills, benzodiazepines or barbiturates that have several and sometimes serious side-effects, such as tachycardia, mucosal dryness, heaviness or amnesia, Jerte Valley cherries may induce sleep without causing side-effects.

29.3 Effect of Jerte Valley cherry-enriched diets on sleep

In recent decades, the hectic lifestyle of industrialized societies has affected the quality of sleep, being a fitting regulation of the sleep-wake cycle an essential factor that determines safety, productivity and healthcare all over the world. Since melatonin and its precursors, the amino acid tryptophan and the indole serotonin have been identified as bioactive compounds in plants (Paredes *et al.,* 2009), the sleep-enhancing effects of these molecules have gained increasingly interest because new perspectives have broadened out for sleep studies. Since both melatonin and its precursors are naturally-occurring compounds found in many vegetables and fruits, some of the beneficial effects produced by the consumption of certain foodstuffs may be due to increased bioavailability of these molecules in the organism. In fact, numerous studies have reflected a close relation between the consumption of vegetables and elevated melatonin concentration in both blood and urine (Nagata *et al.,* 2005; Reiter *et al.,* 2005), such an increase being suggested as the cause of the sleepiness sometimes felt after the midday meal (Bubenik, 2002). As stated before, both tart and sweet cherries are an important source of phytochemicals and reportedly have health-promoting qualities (McCune *et al.,* 2011). The vast majority of studies related to the physiological effects derived from the consumption of cherries are mainly based on the wide range of phenolic and flavonoid compounds, mainly anthocyanins, present in this fruit. However, once the indole melatonin was detected and quantified in cherries, particularly in Montmorency and Balaton tart cherry cultivars (Burkhardt *et al.,* 2001), it was suggested that the physiological benefits provided by the consumption of cherries could be also due to the antioxidant and anti-inflammatory properties of melatonin. First studies concerning melatonin in cherries did not take into account that this molecule could also act as a synchronizer of sleep-wake cycle. Once melatonin and its precursors, the amino acid tryptophan and the indole serotonin, were detected

in cherries, particularly in Jerte Valley sweet cherries (Cubero *et al.,* 2010; González-Gómez *et al.,* 2009), current studies have focused on the relation between cherries and sleep. At this respect, Jerte Valley cherries have been demonstrated not only to ameliorate, but also to prevent sleep disorders. Thus, Garrido *et al.* (2010) measured seven sleep parameters, namely, sleep efficiency, actual sleep time, number of awakenings, total nocturnal activity, sleep latency, assumed sleep and immobility in humans, in order to analyse the effect of the consumption of 200 g twice a day (at lunch and dinner desserts) of seven different Jerte Valley cherry cultivars (Bourlat, Navalinda, Van, Ambrunés, Pico Limón, Pico Negro and Pico Colorado) on sleep quality. For this purpose, an actigraphic monitoring was used to record and display the temporal patterns of the individual's activity and rest. The study showed that the intake of different Jerte Valley cherry cultivars, being analyzed separately, improved the sleep quality in general in both middle-aged and elderly healthy subjects, i.e. individuals without major sleep disturbances (Figure 29.1). These findings are in accordance with several studies demonstrating that the supplementation with tryptophan and/or melatonin produce important sleep-promoting effects not only in subjects with sleep disturbances, but also in subjects who manifested no sleep complaint (Aparicio *et al.,* 2007; Hugues and Badia, 1997). Therefore, Jerte Valley cherries may be an appropriate candidate to ameliorate sleep disturbances due to its high content in tryptophan, serotonin and melatonin (Cubero *et al.,* 2010; González-Gómez *et al.,* 2009), since reduction in the bioavailability of serotonin as a consequence of a low ingestion of dietary tryptophan during the day may also cause alterations in nocturnal rest (Arnulf *et al.,* 2002). Apart from improving sleep quality, the ingestion of seven different cultivars of Jerte Valley cherries has been reported to enhance urinary aMT6s levels in first-void morning urines from middle-aged and elderly subjects (Garrido *et al.,* 2010). Urinary aMT6s is the main urinary metabolite of the indole melatonin and it is considered to accurately reflect the nocturnal melatonin concentration. For this reason, aMT6s determination is commonly used as an indirect evidence for assessing melatonin circulating levels. As shown in Table 29.1, in most cases, after the ingestion of different Jerte Valley cherry cultivars, the highest increases of urinary aMT6s levels were observed in the elderly group. Given that melatonin secretion wanes with age, which has been suggested as one of the main causes for increased sleep disruption in elderly people (Haimov *et al.,* 1994), these results seem to be greatly important as the Jerte Valley sweet cherries may mitigate the decline in melatonin production particular to increasing age.

Recently, the beneficial effects on regulation of sleep-wake cycle provided by the ingestion of Jerte Valley cherries have been reinforced with the assay of a natural product (patent no. ES 2342141 B1) made with different Jerte Valley cherry varieties (Garrido *et al.,* 2009). The inclusion of this cherry-based product in the diet of young, middle-aged and elderly healthy individuals, once again, improved the sleep quality of these subjects, especially, in terms of actual sleep time, total nocturnal activity and immobility (Table 29.2). Moreover, the consumption of this cherry-based product caused a significant increase in circulating melatonin levels, as indirectly measured by urinary aMT6s, in all age groups studied with respect to their corresponding basal values (Table 29.3).
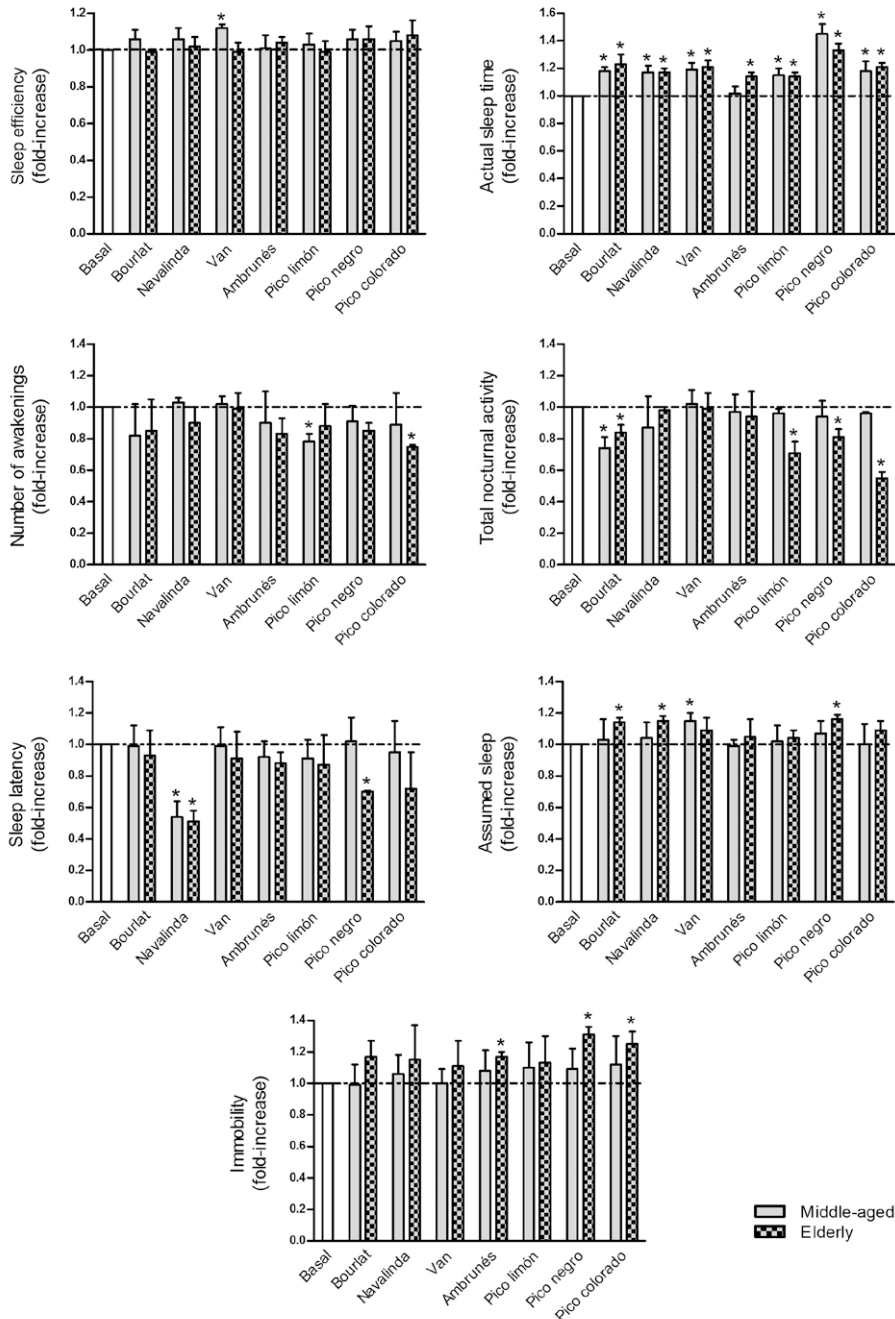
Figure 29.1. Effect of the intake of different Jerte Valley cherry cultivars on sleep parameters in basal (before the intake of Jerte Valley cherry cultivars) and assay (after 3 days of intake of 200 g of different cherry cultivars) conditions in both middle-aged and elderly participants. Each value represents the mean ± SD of six volunteers (after Garrido *et al.*, 2010).

*$P<0.05$ regarding their corresponding basal values.

Table 29.1. Effect of the intake of different Jerte Valley cherry cultivars on urinary 6-sulfatoxymelatonin (aMT6s) levels, measured as nanogram aMT6s per milligram creatinine, in basal (before the intake of Jerte Valley cherry cultivars) and assay (after 3 days of intake of 200 g of different cherry cultivars) conditions in both middle-aged and elderly participants. Each value represents the mean ± SD of six different volunteers, and is expressed in percentage, with 100% being the value obtained in basal conditions (after Garrido *et al.,* 2010).

	Urinary aMT6s levels (% from basal)	
	Middle aged	Ederly
Bourlat	121.5±9.2[*]	144.4±5.3[*#]
Navalinda	113.4±5.1[*]	126.3±6.7[*#]
Van	120.2±3.8[*]	112.7±4.5[*]
Ambrunés	158.4±4.3[*]	169.4±3.8[*#]
Pico Limón	130.1±8.6[*]	118.1±6.2[*]
Pico Negro	165.4±6.3[*]	142.3±3.6[*]
Pico Colorado	143.2±7.9[*]	185.3±3.9[*#]

[*]$P<0.05$ with respect to the corresponding basal values.
[#]$P<0.05$ with respect to the corresponding values obtained in the middle-aged participants.

Table 29.2. Effect of the intake of the Jerte Valley cherry-based product on sleep parameters in basal (before the intake of the cherry product) and assay (after a 3-day intake of the cherry product) conditions in young, middle-aged and elderly participants. Each value represents the mean ± SD of six different volunteers (after Garrido *et al.,* 2009).

	Young		Middle aged		Elderly	
	Basal	Assay	Basal	Assay	Basal	Assay
Sleep efficiency (%)	81.3±2.2	85.2±1.8	86.1±1.2	88.3±2.3	78.9±3.0	80.2±3.0
Actual sleep time (min)	352.6±0.8	396.0±1.1[*]	396.6±0.1	426.0±1.1[*]	357.0±0.9	422.0±1.0[*]
Number of awakenings	8.0±0.9	8.0±1.9	16.0±2.6	14.3±2.0	13.0±2.0	11.0±1.8
Total nocturnal activity (activity pulses)	5,516.0±2.2	4,149.0±2.4[*]	5,908.6±3.5	5,345.0±3.8	6,701.3±2.7	5,905.0±1.5[*]
Sleep latency (min)	10.0±0.7	10.0±1.6	15.0±3.9	12.6±2.6	26.0±3.0	21.6±2.7
Assumed sleep (min)	409.3±2.5	451.3±4.3	428.0±4.1	486.6±2.0	405.0±1.7	496.0±1.2[*]
Immobility (min)	322.0±2.2	361.0±0.8[*]	380.6±4.3	414.0±4.1	282.7±2.1	356.4±2.4[*]

[*]$P<0.05$ with respect to their corresponding basal values.

Table 29.3. Effect of the intake of a Jerte Valley cherry-based product on urinary 6-sulfatoxymelatonin (aMT6s) levels, expressed as a nanogram aMT6s per milligram creatinine, in basal (before the intake of the cherry product) and assay (after a 3-day intake of the cherry product) conditions in young, middle-aged and elderly participants. Each value represents the mean ± SD of six different volunteers (after Garrido *et al.,* 2009).

	Urinary aMT6s levels (ng/mg creatinine)	
	Basal	**Assay**
Young	95.6±7.8	279.2±8.3[*]
Middle aged	62.3±5.7	142.6±19.3[*]
Elderly	40.4±3.4	87.2±2.3[*]

[*]$P<0.05$ with respect to their corresponding basal values.

In addition to humans, the Jerte Valley cherry-based product has been assayed in ringdoves (animals with a diurnal chronotype) and rats (animals with nocturnal chronotype) as well. Thus, it has been reported that the ingestion of the cherry-based product enhanced melatonin and serotonin circulating levels both in young and old animals irrespective of its chronotype (Delgado *et al.,* 2012). In this study, it was also observed an internal desynchronization in melatonin and serotonin basal levels with increasing age since basal concentrations of these indoles were much lower in old animals compared to young animals (Table 29.4). Strikingly, the consumption of the Jerte Valley cherry-based product contributed to resynchronize the circulating levels of melatonin and serotonin in old animals regardless of its chronotype (Table 29.4). Moreover, it was demonstrated that the ingestion of the Jerte Valley cherry-based product reinforced the activity/ rest rhythm of rats and ringdoves (Delgado *et al.,* 2011). On the one hand, the diurnal activity of both young and old rats substantially decreased, whereas their nocturnal activity significantly rose after the intake of the cherry-based product (Figure 29.2). On the other hand, the cherry-based product largely elevated the diurnal activity and remarkably enhanced the nocturnal rest of young and old ringdoves (Figure 29.3). These findings are consistent with previous works reporting that, in diurnal species, i.e. ringdoves, nocturnal melatonin secretion coincides with the habitual hours of sleep, in contrast to nocturnal animals, i.e. rats, that are at the peak of their activity while producing melatonin (Zhdanova, 2005). Thus, the reinforcement of the locomotor rhythm derived from the ingestion of the Jerte Valley cherry-based product may be due to the incorporation of melatonin and/or its related indolic compounds into the organism.

Table 29.4. Serum melatonin and serotonin concentrations in control conditions and after a 10-day treatment with a Jerte Valley cherry-based product in young and old rats and ringdoves. Data are expressed as mean ± SEM of ten animals (after Delgado *et al.*, 2012).

	Rats	Ringdoves
Serum melatonin levels (pg/ml)		
young		
control	190.0±13.8[#]	250.0±24.8[#]
treated	270.0±23.2[*#]	500.0±36.2[*#]
old		
control	125.0±16.1	80.0±19.5
treated	180.0±34.4[*]	250.0±25.8[*]
Serum serotonin levels (ng/ml)		
young		
control	215.0±7.0[#]	1,900.0±120.0[#]
treated	270.0±10.0[*#]	2,300.0±75.0[*#]
old		
control	179.0±5.0	1,500.0±90.0
treated	200.0±7.0[*]	1,845.0±70.0[*]

[*]$P<0.05$ regarding its corresponding values in the control group.
[#]$P<0.05$ regarding its corresponding values in the old animals.

29.4 Concluding remarks

Jerte Valley cherries are a source of phytochemicals with health-promoting effects. The discovery that melatonin, a direct free radical scavenger and an indirect antioxidant, and its related compounds, tryptophan and serotonin, are contained in these fruits has greatly broadened the potential of Jerte Valley cherries from a nutritional point of view. Given the involvement of the afore-mentioned molecules in sleep regulation, the utility of supplementing the diet with cherry fruits in terms of sleep amelioration has been tested. The intake of Jerte Valley cherries produced beneficial effects on sleep-wake rhythms in both middle-aged and elderly participants. Similarly, the ingestion of a Jerte Valley cherry nutraceutical increased significantly the actual sleep time and immobility, and decreased significantly the total nocturnal activity in young, middle-aged, and elderly humans. In rats and ringdoves, animals with nocturnal and diurnal habits, respectively, cherry administration restored the amplitude of the activity rhythm in the old animals to that of the non-treated young groups and significantly increased the serum levels of melatonin in both species and groups of age. Also, human urine antioxidant capacity and animal serum antioxidant capacity increased after Jerte Valley cherry consumption. Based on these experimental data, Jerte Valley cherries may be seen as a potential nutraceutical tool to consolidate sleep and counteract oxidation.
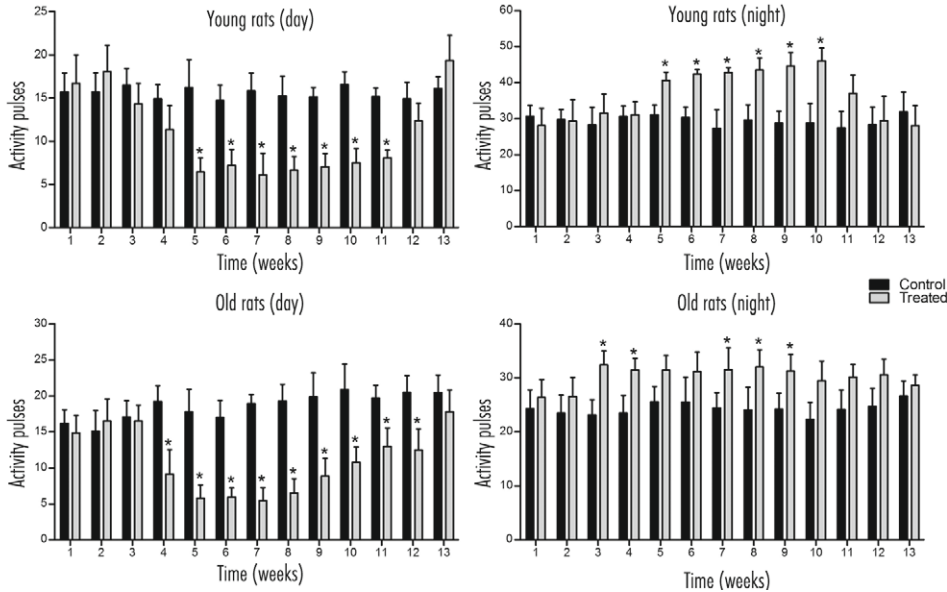
Figure 29.2. Diurnal and nocturnal activity pulses of young and old rats in control conditions, during a 10-day treatment with a Jerte Valley cherry-based product, and 3 days after its termination. Each value represents the mean ± SEM of sixteen determinations (after Delgado *et al.,* 2011).
*P<0.05 regarding their corresponding values in the control group.
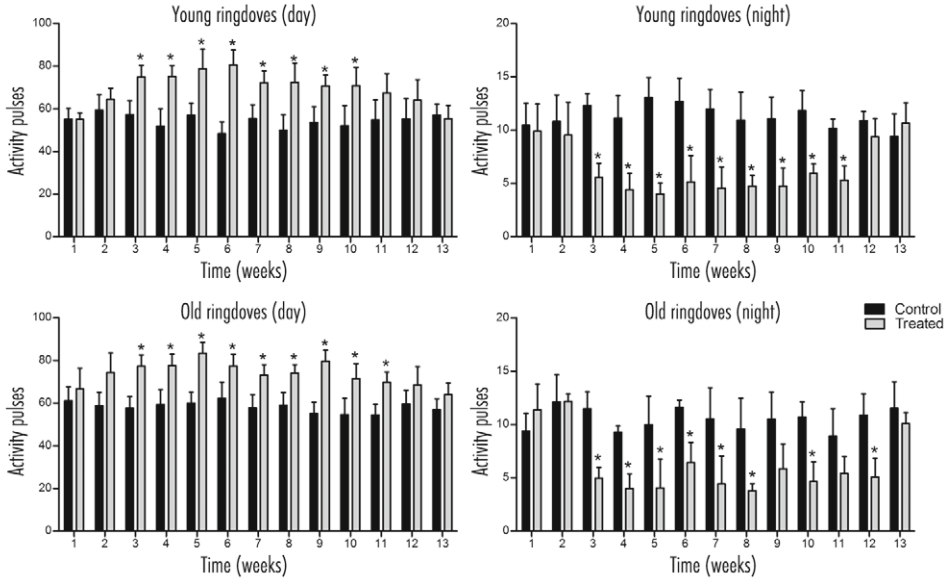
Figure 29.3. Diurnal and nocturnal activity pulses of young and old ringdoves in control conditions, during a 10-day treatment with a Jerte Valley cherry-based product, and 3 days after its termination. Each value represents the mean ± SEM of sixteen determinations (after Delgado *et al.,* 2011).
*P<0.05 regarding their corresponding values in the control group.

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Summary points

- In a small, cross-over study a tart cherry juice was associated with statistically significant improvements in self-reported sleep among older adults with insomnia.
- Compared to placebo, subjects drinking tart cherry juice for two weeks reported less severe insomnia and a reduction in time awake following sleep onset of approximately 19 min compared to the same subjects drinking a placebo beverage for two weeks.
- The magnitude of between-group effects were small to moderate in favor of the tart cherry juice.
- Two other recent studies of healthy sleepers have demonstrated that cherries augment melatonin levels, a plausible mechanism of action.
- Whether tart cherries do promote sleep in sleep disordered patients remains to be fully established.
- If cherries are sleep-promoting, whether melatonin is the pathway by which sleep improvements are achieved requires further study as well.

30. Effect of tart cherry juice beverage on insomnia

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Abstract

There is some preliminary indication that tart cherries may improve sleep in healthy adults. This chapter focuses on the use of a tart cherry juice blend to improve sleep in patients with an actual sleep disorders, namely insomnia. The pilot study reviewed was a small randomized trial using a cross-over design where each participant received both a cherry juice blend a and placebo beverage for two weeks with a two week wash-out period between conditions. Fifteen older adults with chronic insomnia were randomized. Sleep was assessed by daily sleep diaries and by the Insomnia Severity Index. The findings were that tart cherry juice was associated with statistically significant improvements in sleep with small to moderate effect sizes. The findings are discussed in terms of their clinical significance, their relation to existing evidence based treatments for insomnia and the nascent literature on possible mechanisms of action.

Keywords: elderly, melatonin, *Prunus cerasus*, sleep, sleep disorders, sleep maintenance

Abbreviations

ISI	Insomnia severity index
SE	Sleep efficiency
SL	Sleep latency
TST	Total sleep time
WASO	Wake after sleep onset

30.1 Introduction to tart cherries and sleep

Tart cherries are purported to have a number of beneficial health effects with an increasing level of evidence supporting these claims. Montmorency tart cherries (*Prunus cerasus*) in particular contain several phytonutrients including the phenolic acids with anthocyanins chief among them (Kim *et al.,* 2005). Anthocyanin levels in tart cherries exceed those found in sweet cherries and other fruits (Wang *et al.,* 1997) and a positive linear relationship between anthocyanin levels in cherries and oxidative stress protection in neuronal cells has been reported (Wang *et al.,* 1999). Tart cherries also contain high levels of anti-inflammatory substances (Kim *et al.,* 2005; Wang *et al.,* 1999) and melatonin (Burkhardt *et al.,* 2001). In human studies, the health benefits of tart cherries include decreasing oxidative stress in healthy older adults (Traustadottir *et al.,* 2008) and marathon runners (Howatson *et al.,* 2010), enhancing muscle recovery (Connolly *et al.,* 2006) and reducing muscle damage (Bowtell *et al.,* 2011) following strength training, reducing muscle pain during running (Kuehl *et al.,* 2010), decreasing circulating levels of inflammatory markers in general (Kelley *et al.,* 2006) and following marathon running (Howatson *et al.,* 2010). Most recently, sleep improvement has been noted following the intake of Jerte Valley sweet cherries (*Prunus avium*; Garrido *et al.,* 2010; see also Chapter 29) and juice blends made from tart montmorency cherries (Howatson *et al.,* 2011: Pigeon *et al.,* 2010).

At least two putative sleep-promoting pathways for tart cherries exist (and these likely apply to some sweet cherries). First, given that a number of inflammatory cytokines are intricately related to the modulation of sleep (Opp, 2004), their presence in tart cherries suggests one potential pathway to sleep enhancement. Second, the relatively high content of melatonin in tart cherries may serve as a source of exogenous melatonin, a substance with proven sleep-regulating properties. For these reasons, and because there had been anecdotal reports of sleep promoting effects of tart cherries, we undertook a small randomized trial to study the effects of a tart cherry juice beverage on patients with a sleep disturbance meeting diagnostic criteria for chronic insomnia (Pigeon *et al.,* 2010).

30.2 Summary of a study investigating tart cherries for insomnia

The study, which is fully described elsewhere (Pigeon *et al.,* 2010), was a randomized, placebo-controlled, double-blind, cross-over trial. The study was conducted at the University of Rochester

Medical Center Sleep & Neurophysiology Research Lab in Rochester, NY, USA following approval from the Institutional Review Board. The study was funded by the manufacturer of a proprietary juice blended from whole Montmorency tart cherries and apple juice (CherryPharm, Inc.; Geneva, NY, USA).

Sixteen of 19 older adults (≥65 years of age) who had insomnia, completed an informed consent process and baseline assessment, met eligibility requirements and were randomized to treatment conditions. Eligibility requirements included a typical bedtime between 9:00 p.m. and 12:00 a.m., a sleep problem frequency > 3 nights/week with a duration ≥6 months, meeting Research Diagnostic Criteria for Primary Insomnia (Edinger *et al.,* 2004), an ISI≥10, and a minimum of 30 minutes of either SL or wake after sleep-onset, no unstable medical or psychiatric illness, screening negative for substances of abuse, no use of sedating or hypnotic medications, no symptoms suggestive of sleep disorders other than primary insomnia and no diagnosis of diabetes or elevated glucose levels on baseline clinical chemistries.

The analyzed sample (one subject lost to follow-up after baseline assessment) consisted of 15 participants (7 female/8 male; mean age of 71.6 [5.4] years; mean body mass index of 25.8 [4.6]). Randomization to one of two treatment conditions (AB vs. BA order of beverage) was achieved in blocks of two with additional stratification by gender. The two beverages were a proprietary juice blended from whole montmorency tart cherries and apple juice and a placebo beverage mixed intended to have similar taste, sugar, acid, soluble solids and visual properties but without the phytonutrient content found in the tart cherry juice blend treatment juice. Both beverages were bottled in identical clear, 8 ounce, polyethylene containers and labeled with identical product labels. Individual bottles were packaged and delivered to the laboratory in cases marker 'A or B' to maintain double-blindedness.

In this cross-over design, the study procedure consisted of four, 2-week periods (a total of 8 weeks) as follows: a 2-week baseline assessment, two weeks of beverage A or B (based on randomization), a two-week wash-out with no study beverages, and two weeks of beverage B or A. Assessments were conducted at baseline, following the first beverage period and following the second beverage period. Participants were instructed to consume one serving of 226.8 gr in the morning between 8-10 a.m. and one serving in the evening 1-2 hrs before bedtime. Participants completed daily sleep diaries throughout the study period and completed the Insomnia Severity Index, the Multidimensional Fatigue Inventory (Smets *et al.,* 1995), the Beck Depression Inventory (Beck *et al.,* 1961), and the Beck Anxiety Inventory (Beck and Steer, 1991) at baseline and following each of the two-week beverage consumption periods. No significant order or period effects were observed in this crossover trial. Therefore, a general linear model for repeated measures was used to test the group (placebo [n=15] vs. treatment juice [n=15]) by time (baseline vs. post-treatment) effects.

30.2.1 Study results

No main effects for time or group were observed. The effect of tart cherry juice in pre-post treatment comparisons were significant for ISI ($P<0.05$), SL ($P<0.05$), WASO ($P<0.01$), TST ($P<0.01$) and SE ($P<0.05$). The magnitude of these changes are depicted in Figure 30.1. The most pronounced improvement was in terms of WASO minutes where there was a reduction from 79 min of average wakefulness per night following sleep initiation to approximately 62 min per night.

In comparison, the effect of the placebo beverage in pre-post comparisons were significant for TST only ($P<0.05$). There were no significant improvements on measures of fatigue, depression or anxiety in either condition.

When the two groups were directly compared, tart cherry juice (compared to placebo) was associated with a significant reduction on the ISI ($P<0.05$) and in WASO ($P<0.01$), with no such findings for SL, TST or SE. The size of the treatment effects for each study beverage is rendered in terms of effect sizes in Figure 30.2. The effects of tart cherry juice on sleep diary variables range from small to moderate. There is a large effect as measured by the ISI, but such self-report instruments do tend to produce much larger effect sizes than sleep diary measures in most insomnia intervention trials.

Perhaps the more telling set of effect sizes is the contrast between the tart cherry juice and the placebo conditions. These between-group effect sizes range from negligible to moderate as shown in Figure 30.3. Finally, in reviewing the study data for purposes of this review, it was found that
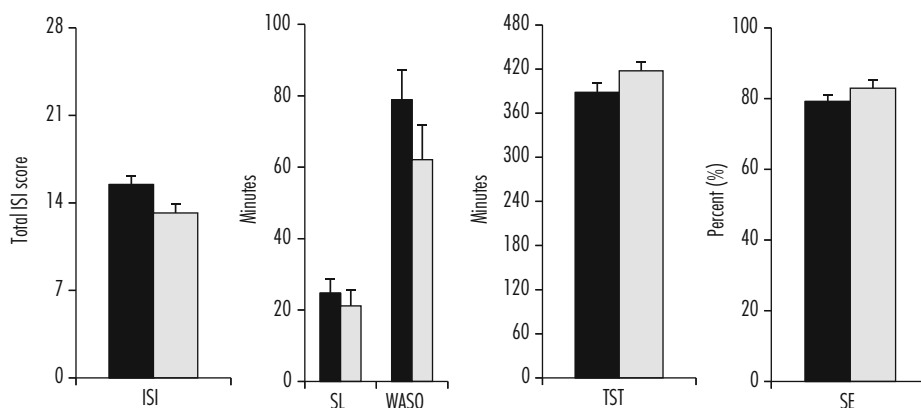
Figure 30.1. Pre-post treatment effects of tart cherry juice in older adults with insomnia.
Dark bars represent pre-treatment values and grey bars represent post-treatment values.
ISI = insomnia severity index; SL = sleep latency; WASO = wake after sleep onset; TST = total sleep time; SE = sleep efficiency.
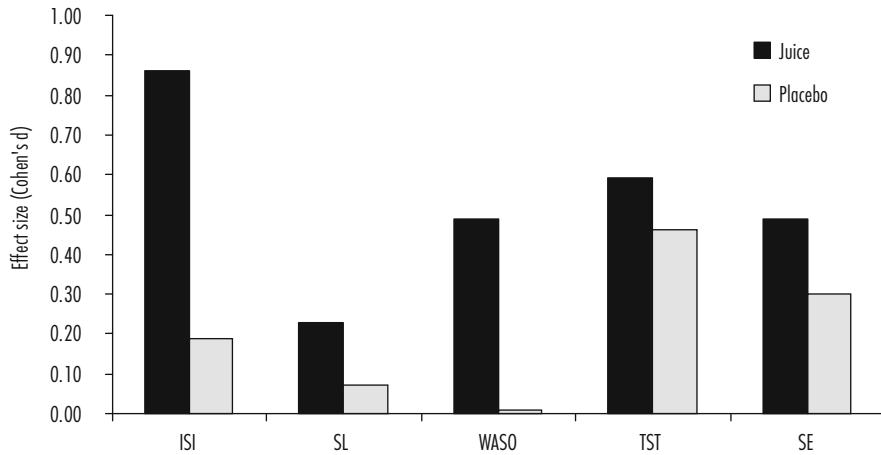
Figure 30.2. Within-group effects of study beverages on sleep.
Juice = tart cherry juice beverage; ISI = insomnia severity index; SL = sleep latency; WASO = wake after sleep onset; TST = total sleep time; SE = sleep efficiency.
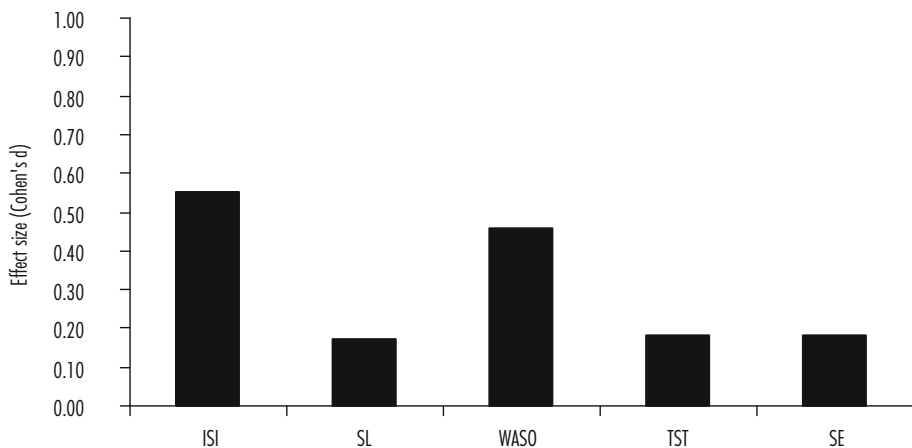
Figure 30.3. Between-group effects of tart cherry juice on sleep.
ISI = insomnia severity index; SL = sleep latency; WASO = wake after sleep onset; TST = total sleep time; SE = sleep efficiency.

following two weeks of tart cherry juice consumption only one of the participants achieved a reduction in the ISI below a total score of 10 and one participant achieved a >7 point reduction on the ISI, which are validated markers of, respectively, clinical insomnia and therapeutic response (Morin *et al.*, 2011).

30.3 Discussion of study findings

Overall, the study established that statistically significant improvements in self-reported insomnia severity and in sleep diary measures of sleep continuity were possible following a two week, twice-a-day administration of a tart cherry juice blend among older adults who had moderate to severe chronic insomnia. In addition to questions about generalizability of the findings due to the sample and lack of objective sleep or biomarker data, several facets of the reviewed study deserve mention. First and foremost this was a pilot study with a small sample size powered to detect moderate between-group differences, which in fact were observed with respect to total ISI score and average WASO. Nonetheless, 15 subjects (serving as their own controls in this crossover study) is a rather small sample from which to draw any sweeping conclusions. Instead, the findings are an indication that a signal is present and that this signal deserves to be further investigated.

30.3.1 Clinical significance of findings

The clinical significance of the findings are modest; their clinical import, therefore, may be fairly questioned. Effect sizes of the tart cherry juice on sleep diary variables (SL, WASO, TST and SE), when compared to placebo, were smaller (0.17. 0.46, 0.18, 0.18 respectively) than meta-analytic norms (Irwin *et al.,* 2006) for behavioral insomnia interventions in older adults (0.51, 0.73, 0.19, 0.38). The mean reduction in WASO, the sleep variable having the largest effect size, of 19 minutes compares to mean reductions of 30 min that are typically observed in both nonpharmacologic and pharmacologic insomnia trials (Smith *et al.,* 2002). Importantly, self-reported insomnia severity, as measured by the ISI, fell from a mean of 15.5 to 13.2 (a 2.3 point reduction compared to a 0.6 point reduction in the placebo condition). In recent randomized controlled trials of cognitive behavioral therapy for insomnia with older adults, mean reductions of 8+ points have been observed on the ISI with effect sizes of 2.0 and greater (Morin *et al.,* 2009). Therefore, to the extent that the effects sizes and the size of clinical gains from this small study are indicative of what can be achieved with tart cherry juice in a clinical sample, those effects are less robust than observed from established insomnia treatments.

On the other hand, the magnitude of improvements exceed those reported for valerian (Taibi *et al.,* 2007), another alternative to standard therapies with anecdotal reports of sleep-promoting effects. Importantly, the observed effects of tart cherry juice do also compare favorably with the use of exogenous melatonin for insomnia, for which meta-analytic mean reductions in WASO compared to placebo are less than 10 minutes (Buscemi *et al.,* 2005). In short, exogenous melatonin, while effective for delayed sleep phase disorders, has some limited value for decreasing sleep onset latency and no effectiveness for WASO. In contrast, tart cherry juice had a moderate effect on WASO in the reviewed study.

30.3.2 Possible mechanisms of action

The preceding section raises a third point of discussion. Namely, by what mechanism might tart cherry juice achieve its modest effects on sleep among chronic insomnia sufferers? As noted in the introduction, the two most probable mechanisms of action are an anti-inflammatory pathway and/or a melatonin pathway. The reviewed study was in no way designed to address this issue, but the findings do raise some questions particularly in conjunction with findings from two important studies conducted in normal healthy sleepers (Garrido *et al.*, 2010).

In these healthy sleeper studies both sweet (Garrido *et al.*, 2010) and tart (Howatson *et al.*, 2011) cherries were associated with very modest sleep improvements in already good sleepers. For instance, non-significant reductions of approximately 5 min in sleep diary measured SL and 1 min in WASO were observed in a cross-over study (n=20) conducted by Howatson and colleagues with similar timing and amount of daily tart cherry juice dosing as the reviewed study. With respect to the study by Garrido *et al.* the uncontrolled study (n=12), seven varieties of sweet cherries were consumed as whole fruits over seven, separate 72 hr periods. Though is not possible to determine actual sleep variable values from the way the data are reported, actigraphy measured sleep improved compared to baseline. Notably, both studies measured urinary melatonin levels (from a morning void in the former and from a 48 hr collection in the latter study) and found increases over basal levels following cherry supplementation. In addition, in their well-controlled study Howatson *et al.* demonstrated an increase in urinary melatonin compared to a placebo condition. Interestingly, as discussed by these authors despite an overall increase in melatonin levels there was no difference in the diurnal rhythm or in amplitude or timing of peak concentrations. Together, these two studies suggest that tart cherry juice and whole sweet cherries each increase melatonin levels in healthy sleepers, making more plausible the possibility that melatonin supplementation may have had a role in the improvement of sleep in the insomnia sample of the reviewed study.

Caution is certainly warranted, however, on several counts. First, the healthy sleeper studies were not shown to alter circadian phase, making it unlikely that the phase-shifting properties of melatonin were at work. In addition, the amount of melatonin intake from the Pigeon *et al.* and Howatson *et al.* studies equate to approximately 0.08 mg, whereas exogenous melatonin doses of 0.3 mg are the lowest doses to have been tested and found to have an impact on sleep (Van Geijlswijk *et al.*, 2010). Moreover, the elimination half-life of melatonin is relatively rapid (<1 hr; Fourtillan *et al.*, 2000), again making phase shifting unlikely, but also making the WASO improvements observed in the insomnia study less likely to be attributable to soporific effects of melatonin in the middle of the night. It is possible, that plasma or salivary measures of melatonin across the 24 hr day may yet show that cherries do shift circadian phase. It is also possible that other mechanisms or pathways to improved sleep underlie the positive signal that remains with respect to cherries and sleep.

30.3.3 Next steps

Certainly, the sleep-promoting effects of tart and/or Jerte Valley cherries warrant continued investigation. Controlled studies in several sleep disordered populations (e.g. delayed sleep phase disorder, sleep initiation insomnia, sleep maintenance insomnia) would be most useful with the addition diurnal measures of both melatonin and anti-inflammatory substances.

Author disclosure statement

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Summary points

- A few cirrhotic patients have sleep disturbance.
- The abnormalities in branched-chain amino acid (BCAA) and aromatic amino acid
- Aromatic amino acids (AAA) levels in liver cirrhosis (LC) are expressed as a molar ratio of BCAA/AAA or BCAA/tyrosine.
- The plasma BCAA concentration may influence brain function.
- BCAA supplementation improves sleep disturbance.
- Sleep disturbance is an early sign of hepatic encephalopathy.
- Peaking of melatonin levels is significantly delayed in cirrhotic patients.
- Restless legs syndrome and obstructive sleep apnoea syndrome are known to be causes of sleep disturbance in chronic liver disease patients.

31. Branched-chain amino acid-enriched snacks for sleep disturbance

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Abstract

Patients with liver cirrhosis (LC) have a variety of symptoms; some of them have sleep disturbance. The mechanism of sleep disturbance in these patients is still unclear. Sleep disturbance is one of the symptoms of overt hepatic encephalopathy but has also been reported for patients without encephalopathy. Recently, attention is being paid to the ratio of branched-chain amino acids (BCAAs) and aromatic amino acids (AAAs) in liver disease patients. Abnormalities in BCAA and AAA levels in LC are expressed as molar BCAA/AAA ratio or BCAA/tyrosine ratio. The plasma BCAA concentration may influence brain function and affect appetite, physical and mental fatigue, mental performance, and physical endurance. The increased influx of AAAs into the brain would increase the biological availability of precursors for neurotransmitters. BCAA-enriched snacks are useful for cirrhotic patients who do not have overt encephalopathy but experience sleep disturbance. BCAA supplementation improved sleep disturbance, and amino acid supplementation without BCAA induced sleep disturbance. It has been considered that sleep disturbance is an early sign of hepatic encephalopathy and symptom of minimal hepatic encephalopathy, which is characterized by cognition dysfunction without overt encephalopathy. Melatonin, a brain hormone and common pacemaker of circadian rhythm, and its metabolite are involved in hepatic metabolism; thus, the reason for sleep disturbance (e.g. delayed sleep phase) might be that peak melatonin levels are significantly delayed in cirrhotic patients. Neurosteroids, which are suggested to be related with hepatic encephalopathy, are known to induce significant alterations of the sleep/wake cycle. BCAAs can act as psychotropic drugs that directly act on the central nervous system. Restless legs syndrome and obstructive sleep apnoea syndrome are known as causes of sleep disturbance in chronic liver disease patients. The cause of sleep disturbance and the relationship between prognosis of LC and sleep disturbance will be the subject of future research.

Keywords: hepatic encephalopathy, cirrhosis, sleep disturbance

Abbreviations

5-HT	5-hydroxytryptamine
AAA	Aromatic amino acid
BCAA	Branched-chain amino acid
EEG	Electric encephalography
ESS	Epworth sleepiness scale
LC	Liver cirrhosis
MHE	Minimal hepatic encephalopathy
PEM	Protein-energy malnutrition
PT	Prothrombin time
TACE	Transarterial chemoembolization

31.1 Introduction

Patients with liver cirrhosis have a variety of symptoms. A few cirrhotic patients have sleep disturbance (Cordoba *et al.,* 1998). In recent years, it has been reported that sleep is closely related to physical and mental health (Bonnet, 1985). Sleep disturbance is one of the symptoms of overt hepatic encephalopathy (Watanabe, 1998), but this has been reported for patients without encephalopathy (Cordoba *et al.,* 1998). Hepatic encephalopathy is a neuropsychiatric disorder. The diagnosis of hepatic encephalopathy is based on clinical presentation (insomnia, lethargy, somnolence, and coma). However, making the diagnosis of subclinical hepatic encephalopathy is more difficult than that of overt hepatic encephalopathy, and many cirrhotic patients have a subclinical disease, e.g. sleep disturbance. Neurosteroids, which are suggested to be related with hepatic encephalopathy, are known to induce significant alterations of the sleep/wake cycle (Ahboucha and Butterworth, 2008). Results of a previous report (Cordoba *et al.,* 1998), in which a questionnaire was used, indicated an elevated number (47.7%) of cirrhotic patients who complained of unsatisfactory sleep compared with healthy controls (4.5%). In addition, the overall sleep quality was significantly lower in the primary biliary cirrhosis group (Newton *et al.,* 2006) and in the non-alcoholic fatty liver disease group (Newton *et al.,* 2008) compared to the control group. In Japan, the overall prevalence of insomnia during the preceding month was 21.4% among the Japanese general population (Kim *et al.,* 2000).

The relationship between sleep disturbance and variegated cirrhosis symptoms is still not clear. Previous reports indicated that sleep disturbance is not related to liver function (Cordoba *et al.,* 1998). It has been reported that fatigue in patients with non-alcoholic fatty liver disease is significant and is associated with excessive daytime sleepiness but not with insulin resistance (Newton *et al.,* 2006). Because of the emergence of sleep disturbance in cirrhotic patients without encephalopathy, the relationship between sleep disturbance and cirrhosis symptoms, excluding encephalopathy, should be examined.

31.2. Liver disease and sleep disturbance

31.2.1 Cirrhosis and metabolic disorder

The energy balance of LC was characterized as PEM, involvement of a glycolytic disorder, reduction in glycogenosis, negative nitrogen balance, and hyper-lipolysis (Muller *et al.,* 1992). PEM carries a high risk of morbidity and mortality by increasing the risk of life-threatening complications, which in turn reduce the quality of life, independent of the liver function (Nielsen *et al.,* 1993). Recently, attention is being paid to the ratio of BCAAs and AAAs in patients with liver disease. Abnormalities in the BCAA and AAA levels in LC are expressed as molar ratio of BCAA/AAA or BCAA/tyrosine. Two studies have shown that administration of BCAA corrected malnutrition associated with LC (Kajiwara *et al.,* 1998). In addition, it has been reported that long-term nutritional BCAA supplementation is useful to prevent hepatic failure and to improve surrogate markers in advanced LC (Marchesini *et al.,* 1990). It has been shown that BCAA supplementation is effective in down-regulating protein metabolism in LC, improving nitrogen balance and, finally, resulting in better clinical outcomes (Moriwaki *et al.,* 2004; Nakaya *et al.,* 2007). It is also been speculated that the mechanisms for the beneficial effects of BCAAs might be mediated by their stimulating activity on hepatocyte growth factor, favouring liver regeneration (Tomiya *et al.,* 2004). Previously, we demonstrated that a BCAA supplement taken orally as a late evening snack prevented suppression of liver function by TACE in patients with LC complicated with hepatocellular carcinoma during the two-week period after TACE (Takeshita *et al.,* 2009). The use of BCAAs in the therapy for hepatic encephalopathy was based on findings that BCAAs facilitate ammonia detoxication by supporting glutamine synthesis in skeletal muscles and the brain, normalize the amino acid concentration, and decrease the brain influx of AAAs. The increased influx of AAAs into the brain would increase the biological availability of precursors for neurotransmitters (Dejong *et al.,* 2007). BCAA levels are crucially determined by nutritional factors, whereas AAA levels appear to depend much more upon the intact hepatic metabolism (Dejong *et al.,* 2007). BCAAs are useful for hepatic malnutrition and encephalopathy (Watanabe, 1998); however, the effect of BCAA administration on sleep disturbance has not been reported. Therefore, we examined the effect of BCAA-enriched snacks on sleep disturbance in cirrhotic patients (Ichikawa *et al.,* 2010).

31.3. Amino acids for sleep disturbance associated with liver disease

31.3.1 BCAA-enriched snacks for improving sleep disturbance

We investigated a total of 21 patients at the Nagasaki University Hospital, including nine men and 11 women, from January to June 2009 (Ichikawa *et al.,* 2010). We constructed questionnaire items for the evaluation of cirrhosis symptoms. The items, as major symptoms of cirrhotic patients, were hand tremor, appetite loss, muscle cramps in the foot, fatigue, decreased strength, anxiety, abdominal fullness, abdominal pain, and a feeling of low energy. We used the ESS for evaluation of daytime hypersomnolence. Energy supplementation of BCAA snacks was performed as late

evening snack. All patients were assessed at study entry, after four weeks and after eight weeks. It was demonstrated that BCAA-enriched snacks taken orally as late evening snack improved the ESS score of cirrhotic patients without encephalopathy. We used a BCAA-enriched snack (Aminoleban EN, Otsuka Pharmaceutical Co., Tokyo) as supplementation for LC patients. The patients received a BCAA snack (50 g) once a day at 22:00 (late evening snack) from day one (at entry) for eight weeks. Aminoleban EN is a snack that contains 13.5 g protein, high levels of BCAA (Fisher ratio: 38), and low levels of other amino acids (210 kcal per 50 g; one pack). Patients in the BCAA group continued taking BCAA snacks for years. In addition, patients in the control group did not take BCAA snacks. Patients were instructed to maintain a diet containing 30-35 kcal and 1.2-1.3 g of protein per kilogram of the ideal body weight per day. In the BCAA group, the patients were educated to adjust their total energy intake by subtracting 210 kcal of the BCAA snack from their meals. In the control group, a rice ball was given as late evening snack, which provided 210 kcal of energy and contained 9 g of protein. The nutritional intake was evaluated in all patients by dieticians at the initial period, after four weeks and after eight weeks. A beneficial result was noted in short term, i.e. at four weeks after beginning of treatment. This study demonstrated the biological availability of BCAA supplementation in cirrhotic patients with sleep disturbance (Figure 31.1). However, although the cirrhotic symptom-related score was positively related with the Child-Pugh score at entry, we were not able to identify the item that is related to the ESS score (Figure 31.2). BCAA-enriched snacks are useful for cirrhotic patients who do not have overt encephalopathy but experience sleep disturbance.

31.3.2 Amino acid challenge for cirrhotic patients

In contrast to our previous report (Ichikawa *et al.,* 2010), the haemoglobin-like amino acid mixture has been reported to be taken orally (Bersagliere *et al.,* 2011). Upper gastrointestinal bleeding is an ammoniagenic and catabolic event, probably due to the absence of isoleucine in the haemoglobin molecule (Dejong *et al.,* 2007). Hyperammonaemia and hepatic encephalopathy can be simulated by an amino acid challenge or the administration of a mixture of amino acids mimicking the composition of haemoglobin (Bersagliere *et al.,* 2011). The aim of their study was to investigate the correlation between clinical, psychometric, and wake-/sleep-EEG findings in induced hyperammonaemia. They found that the amino acid challenge led to a significant increase in daytime subjective sleepiness and changes in the EEG architecture of a subsequent sleep episode in patients with cirrhosis, indicating a reduced ability to produce restorative sleep.

31.3.3 Role of amino acids for sleep

It was recently demonstrated that BCAA snacks, taken orally as late evening snack, improved the ESS score of cirrhotic patients without encephalopathy (Ichikawa *et al.,* 2010). This study demonstrated the availability of BCAA supplementation for cirrhotic patients with sleep disturbance. However, although the cirrhotic symptom-related score was positively related with the Child-Pugh score at entry, we were not able to identify the item that is related to the ESS score. In contrast, amino acid challenges induced sleepiness (Bersagliere *et al.,* 2011). These findings
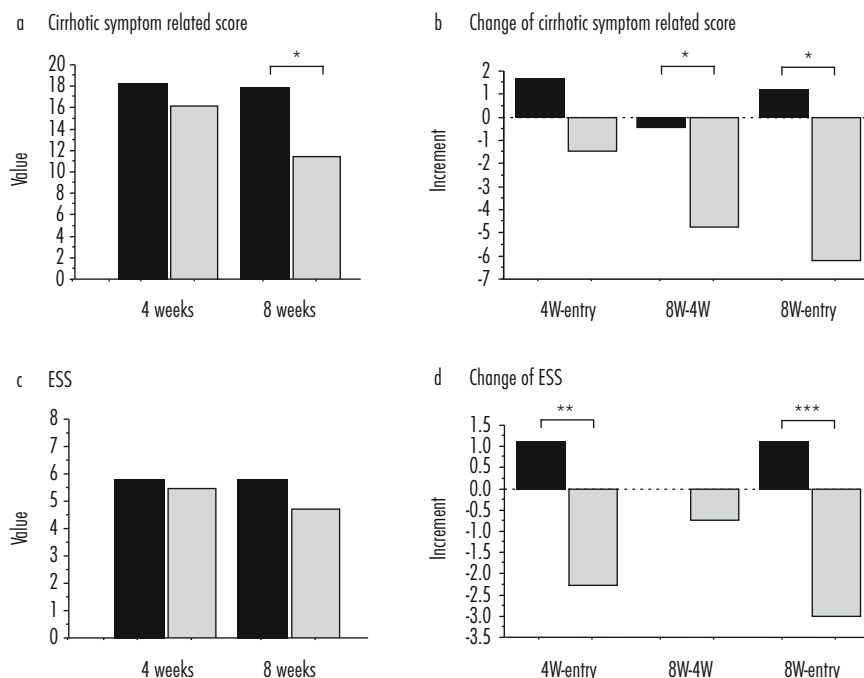
Figure 31.1. Transition of cirrhotic symptom-related score and Epworth Sleepiness Scale (ESS) score during the follow-up period. Values of cirrhotic symptom-related score (a) and ESS (b) at four weeks and eight weeks. Change of cirrhotic symptom-related score (c) and ESS (d). '4W-entry' is presented as an increment value in which the data of pre-treatment are subtracted from the data of four weeks after the beginning of observation. '8W-entry' and '8W-4W' were calculated as increment between the two indicated periods. Black boxes represent the mean value in the observation group. Gray boxes represent the mean value in the branched-chain amino acid (BCAA) group (Ichikawa *et al.*, 2010).
*P<0.1; **P<0.05; ***P<0.01.

have important clinical implications. BCAA supplementation improved sleep disturbance, and amino acid supplementation without BCAA induced sleep disturbance.

31.3.4 Sleepiness of cirrhotic patients

The frequency of sleep disturbance in cirrhotic patients could not be evaluated in our study (Ichikawa *et al.*, 2010), because we did not include a normal healthy control group. An ESS score of 10 or more, which is a significant marker of daytime hypersomnolence, was found in five of 21 cirrhotic patients (23.8%); the mean ESS score was 6.38 in this study. In a previous Japanese report (Suzuki *et al.,* 2008), the mean ESS score was 5.6 in 144 healthy control cases and was lower than that in the Parkinson's disease group. In an Italian study (Mostacci *et al.,* 2008), cirrhotic patients had a mean ESS score of 6.66 (6.17 in healthy control), and 15.7% of them had an ESS score higher than 10 (12.9% in healthy controls). In a primary biliary cirrhosis study (Newton *et*
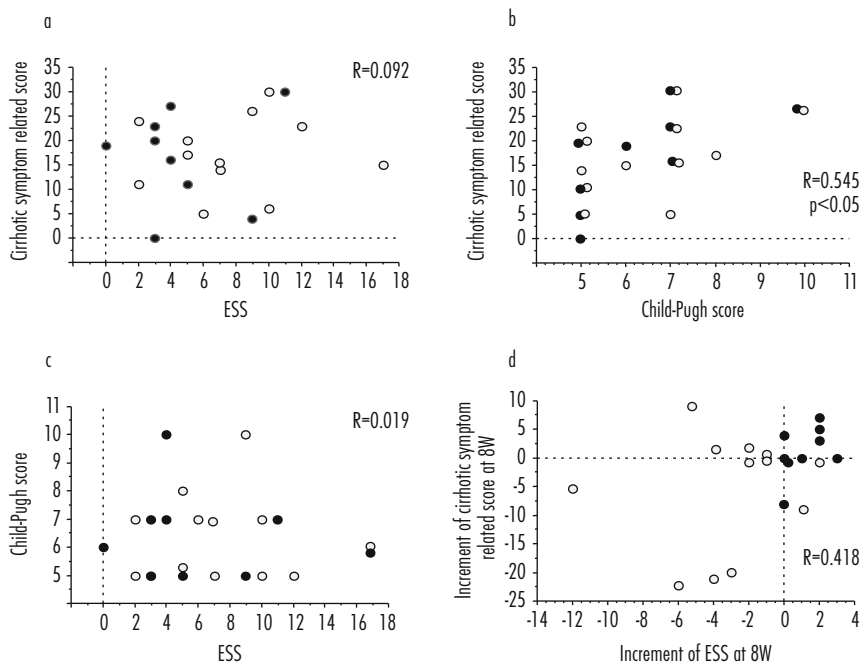
Figure 31.2. A scatter graph is used to examine the relationship between cirrhotic symptom-related score and Epworth Sleepiness Scale (ESS) (a), cirrhotic symptom related-score and Child-Pugh score (b), Child-Pugh score and ESS score (c), and increment of the cirrhotic symptom-related score from eight weeks after entry to entry and increment of the ESS score from eight weeks after entry to entry (d). The increment value was calculated as the difference between the value at eight weeks after entry and the value at entry. Black circles indicate patients in the observation group. Gray circles indicate patients in the branched-chain amino acid (BCAA) group. 'R' is the correlation coefficient. The cirrhotic symptom-related score and Child-Pugh score showed a statistically significant positive correlation (Ichikawa *et al.*, 2010).

al., 2006), patients had a mean ESS score of nine (5 in healthy controls), and more than 50% of them had an ESS score higher than 10 (15% in healthy controls). We think that our ESS data of cirrhotic patients are not very different from those of previous studies. In addition, all patients with significant daytime hypersomnolence improved by administration of BCAA-enriched snacks in our study (Ichikawa *et al.,* 2010).

31.4 What is the mechanism of sleep disturbance in hepatic encephalopathy?

The mechanism of sleep disturbance in cirrhotic patients is still unclear. Thus far, it has been considered that sleep disturbance is the early sign of hepatic encephalopathy and symptom of MHE, which is characterized by cognition dysfunction without overt encephalopathy (Bajaj, 2008). There is no current consensus on how MHE should be diagnosed. However, the following

requirements need to be met to confirm a diagnosis of MHE: 1. normal mental status on clinical examination, 2. documentation of neurological impairment by multiple methods, and 3. exclusion of other disturbances that may cause neurological impairment (Ortiz *et al.,* 2005). In an amino acid challenge study (Bersagliere *et al.,* 2011), subjective sleepiness may be a useful surrogate marker of hepatic encephalopathy. In our study (Ichikawa *et al.,* 2010), patients had a normal mental status and did not have other neurological impairments; however, the patients' subclinical cognitive function had not been documented. Therefore, our patients could not be diagnosed as having MHE. However, we think that an adequate evaluation of the relationship between MHE and sleep disturbance is necessary. Previous reports described that the psychometric test was not correlated with the ESS score (Vignatelli *et al.,* 2001); there was no relationship between sleep and cognitive performance either at baseline or in relation to treatment (Spahr *et al.,* 2007). There is a positive correlation between HME and Child-Pugh score (Ortiz *et al.,* 2005), but not between sleep disturbance and Child-Pugh score (Cordoba *et al.,* 1998). In our study (Ichikawa *et al.,* 2010), the ESS score was not related with liver function and cirrhotic symptom-related score. It has been considered that MHE is a part of the cause of sleep disturbance in cirrhotic patients, but we think that there is another inducer of sleep disturbance. Other groups speculated that there is a relationship between sleep disturbance and MHE and that the mechanism of sleep disturbance in cirrhotic patients is deterioration of the circadian rhythm (Bajaj, 2008; Cordoba *et al.,* 1998). In particular, melatonin, a brain hormone and common pacemaker of the circadian rhythm, and its metabolites are involved in the hepatic metabolism; thus, the reason for sleep disturbance (e.g. delayed sleep phase) might be because peak melatonin levels are significantly delayed in cirrhotic patients (Steindl *et al.,* 1995). In contrast, it has been reported that cirrhosis does not shift the circadian phase of plasma fibrinolysis (Piscaglia *et al.,* 2002). Because we did not evaluate the sleep phase in our cirrhotic patients, it is necessary to evaluate abnormal circadian variations in the future. However, we learnt that BCAA snacks are effective for sleep disturbance in cirrhotic patients. Levels of tryptophan, an AAA, are elevated in cirrhotic patients; tryptophan is the precursor for the neurotransmitter 5-HT, which is involved in fatigue and sleep (Castell *et al.,* 1999; Newsholme and Blomstrand, 2006). In a previous report (Castell *et al.,* 1999), it has been suggested that BCAA supplementation may help to counteract the effects of an increase in plasma free tryptophan. It has been suggested that the plasma BCAA concentration may influence brain function and affect appetite, physical and mental fatigue, mental performance, and physical endurance. In another report, it has been shown that oral intake of BCAAs may reduce tryptophan uptake and 5-HT synthesis and release, thereby delaying fatigue (Newsholme and Blomstrand, 2006). Recently, it has been reported that fatigue in patients with liver disease is significant and associated with excessive daytime sleepiness and high average ESS scores (Newton *et al.,* 2008). In our study (Ichikawa *et al.,* 2010), the ESS score was not related with the cirrhotic symptom-related score and the Child-Pugh score, but it would be important to examine the participations of other factors such as fatigue, which have not been evaluated in this study.

It is necessary to verify the biological availability of orally administered BCAA snacks in cirrhotic patients with sleep disturbance. A previous report showed that BCAAs can act as psychotropic drugs that directly act on the central nervous system (Watanabe, 1998). The primary function of the liver is to regulate the amino acid supply to peripheral tissues. The balance of the physiologic

amino acid concentration is altered in patients with an increased BCAA/AAA ratio. In addition to hepatic encephalopathy, restless legs syndrome and obstructive sleep apnoea syndrome are known as causes of sleep disturbance in cirrhotic patients (Franco *et al.*, 2008; Newton *et al.,* 2008). The cause of sleep disturbance and the relationship between prognosis of LC and sleep disturbance will be the subject of future research.

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Summary points

- Nucleotides in breast milk are important for newborn development.
- Levels of these nucleotides show circadian rhythms in breast milk.
- Many of the nucleotides have been shown to regulate sleep in humans.
- The patterns of nucleotide levels support their roles in sleep/awake function.
- More research needs to investigate the underlying mechanism and relative importance of the nucleotides in sleep function and normal development of infants.

32. Human milk nucleotides improve sleep: a focus on circadian profiles

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Abstract

Human milk and the milk of several mammalian species contain nutrients, anti-infectious and immunocompetent substances and nucleotides into the non-protein fraction. These compounds are involved in several different functions, and although changes in the concentrations of some breast milk components over the course of the day are already well described, until now little is known about the nature and underlying cause of the circadian pattern. This chapter will explain the roles of the nucleotides in the sleep/wake cycle and will discuss the circadian oscillations of the concentration of these substances in human breast milk.

Keywords: circadian, breast milk, nucleotides, sleep, wake, newborn

C.L. Sánchez, C. Barriga, A.B. Rodríguez and J. Cubero

Abbreviations

5'AMP	Adenosine 5' monophosphate
5'CMP	Cytidine 5' monophosphate
5'GMP	Guanosine 5' monophosphate
5'IMP	Inosine 5' monophosphate
5'TMP	Thymidine 5' monophosphate
5'UMP	Urine 5' monophosphate
cGMP	Cyclic guanosine monophosphate
NO	Nitric oxide
REM	Rapid eye movement

32.1 Introduction

Breast milk is the ideal and natural food for newborn infants during the first six months of life as it supplies all the necessary requirements for the development of a baby (WHO, 2003).

Human milk and the milk of several mammalian species contain nutrients and anti-infectious agents and immunocompetent substances, as well as a group of biologically active substances called 'milk-borne trophic factors' or 'growth modulators'. Milk-borne trophic factors can be classified into three groups: hormones and trophic peptides; nucleotides, nucleosides and derived substances; and polyamines. These trophic factors could exert a cytoprotective effect against toxins and reduce the potential risk of bowel undergo necrosis in infants (Britton *et al.*, 1991; Koldovsky, 1994).

Human milk contains high levels of nucleotides, which are the precursors of nucleic acids. Nucleotides function as building blocks that can enhance the regenerative growth and differentiation of several organs and tissues, especially in the liver. Nucleotides from milk enhance lipid metabolism, lipoprotein synthesis and liver cell function and regeneration (Sanchez-Pozo *et al.*, 1994). Nucleotides also have a crucial impact on the development of the gut associated lymphoid tissue (Buts, 1998).

These compounds are involved in several functions including cell division, cell growth, and modulation of the immune system (Janas and Picciano, 1982; Johke, 1963). These nucleotides in breast milk may help maintain the intestinal health in newborns, and reduce the incidence of enteric diseases. Dietary nucleotides have been shown to decrease the prevalence of diarrhea in human infants by reducing stool pH could reduce the growth of pathogenic bacteria and hence the incidence of infectious diarrhea. Animals also require nucleotides to respond to immunological challenges (Carver *et al.*, 1995; Donovan and Lönnerdal, 1989).

32.2 Nucleotides effects on the sleep/wake cycle

Nucleotides are built by a pentose (carbohydrate), a nitrogen-containing base and a phosphate group. Depending on the base, these substances can be divided in two types: purines (Figure 32.1) and pyrimidines (Figure 32.2). The 5'nucleotide derivative is the principal form of cellular purines and pyrimidines. The commonest purines are 5'AMP, 5'GMP, as well as their precursor, 5'IMP. On the other hand, the major pyrimidines are 5'CMP, 5'UMP and 5'TMP. These purines and pyrimidines can be synthesized de novo in the liver, but this metabolic process requires a high energy demand in form of ATP. An alternative mechanism is to convert the free purine

Adenosine 5'monophosphate   Guanosine 5'monophosphate   Inosine 5'monophosphate
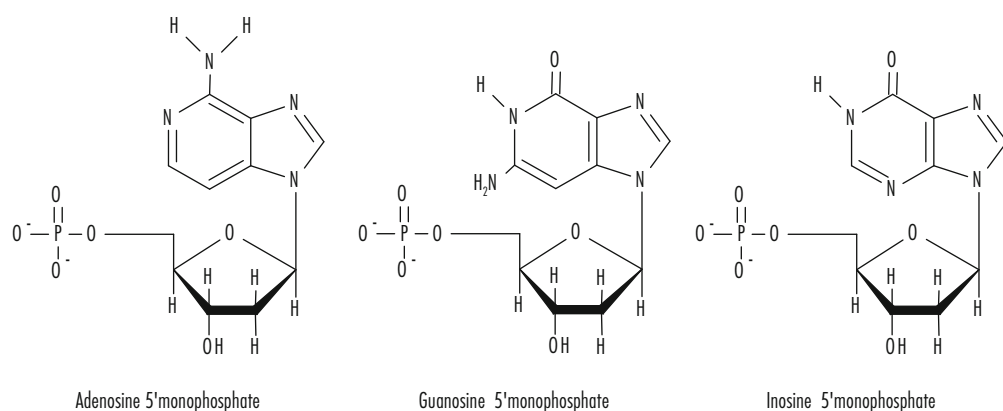
Figure 32.1. Chemical structures of the purine nucleotides. Adenosine 5'monophosphate (5'AMP), guanosine 5'monophosphate (5'GMP) and the key precursor of the purine metabolism, inosine 5'monophosphate (5'IMP).

Thymidine 5'monophosphate   Cytidine 5'monophosphate   Uridine 5'monophosphate
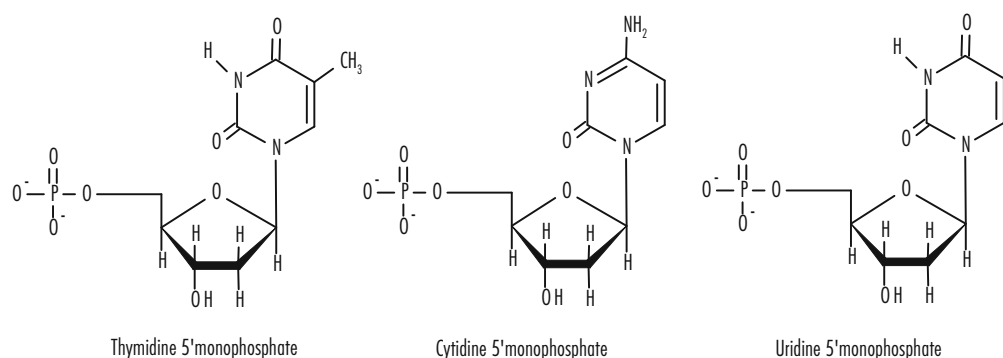
Figure 32.2. Chemical structures of the pyrimidine nucleotides. Thymidine 5'monophosphate (5'TMP), cytidine 5'monophosphate (5'CMP) and uridine 5'monophosphate (5'UMP).5'monophosphate (5'GMP) and the key precursor of the purine metabolism, inosine 5'monophosphate (5'IMP).

and pyrimidine bases and nucleosides (same structure as nucleotides without the phosphate group) to nucleotides.

Although oscillations in the concentration of some of the breast milk components have already been well described (e.g. fats), until now little was known about the nature and etiology of the circadian pattern of nucleotides (Sanchez *et al.*, 2009). A previous study reported that some of the immune functions of nucleotides contained in breast milk play a role in regulating sleep/wake function (Zielinski and Krueger, 2011).

Circadian rhythms are ubiquitous in eukaryotes and have been reported in a wide variety functions such as biological timing, activity/rest cycles, hormone secretion, reproductive cycles in some species, etc. This daily timekeeping is driven by transcriptional/translational feedback loops, whereby rhythmic expression of 'CLOCK' gene products regulates the expression of associated genes in approximately 24-hr cycles (O'Neill *et al.*, 2011). Recently, a metabolomics study has shown that synthesis and degradation of nucleotides in the liver are under transcriptional circadian control (Fustin *et al.*, 2012).

32.2.1 Purines

Adenosine 5' monophosphate

Among the nucleotides, 5'AMP (Figure 32.1) has been the most frequently cited as a sleep inducer in the literature over the past 30 years. 5'AMP has been implicated in several aspects of the sleep function. Extracellular oscillations in 5'AMP have been demonstrated and are due to fluctuations in the secondary messenger cyclic adenosine monophosphate (Dunwiddie and Worth, 1982). 5'AMP also regulates both REM and non-REM sleep in the preoptic area neurons (Radulovacki, 1985; Virus *et al.*, 1983). The administration of 5'AMP induces a hypnotic effect and the levels of 5'AMP decline during the period of wakefulness, suggesting a circadian rhythm in 5'AMP concentrations (Porkka-Heiskanen *et al.*, 2002).

Concentration of 5'AMP in human breast milk demonstrates a circadian rhythm, with a peak in concentration (acrophase) during the dark period (Figure 32.3). This peak in 5'AMP during the night may similarly induce sleep in infants naturally (Sánchez *et al.*, 2009). A 5'AMP-enriched 'nighttime' formula of artificial breast milk has been shown to induce sleep in newborn infants (Cubero *et al.*, 2006).

Guanosine 5' monophosphate

Another purine nucleotide contained in breast milk, 5'GMP (Figure 32.1), and its cyclic form (cGMP) has been to regulate sleep. cGMP mediates most of the neuronal effects of NO. NO in neurons of the pontine tegmentum facilitates sleep, particularly rapid-eye-movement sleep. NO within the laterodorsal tegmentum intervenes in modulating neuronal firing through an auto-inhibitory process involving the co-synthesized neurotransmitters (Gautier-Sauvigné *et al.*,
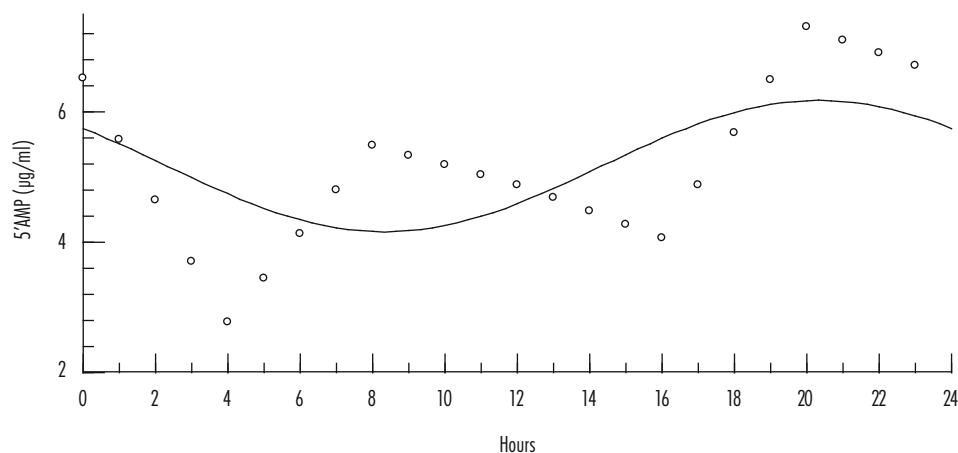
Figure 32.3. This graph depicts the fluctuations of adenosine 5'monophosphate levels (5'AMP) during 24-hrs. Circadian rhythm is shown by a sinusoidal curve. (Sanchez *et al., 2009*).

2005). Other evidences that relate 5'GMP to sleep function include increased wakefulness and the suppression of REM and non-REM sleep following injections of a cGMP inhibitor in rats; clinical studies have shown that cGMP plasma concentrations rise when the subject goes to bed and remain high throughout the night. This observation may due to cGMP's ability to simulate the secretion of the pineal hormone melatonin, a critical regulator of sleep induction (Ribeiro *et al.*, 2005; Zhdanova *et al.*, 1999). In support of a sleep-inducing function, 5'GMP levels in breast milk shows a circadian rhythm with increasing levels during the nocturnal period, until a peak concentration is reached at the end of the night (Figure 32. 4) (Sánchez *et al.*, 2009).

Inosine 5'monophosphate

The 5'IMP (Figure 32.1) is synthesized from 5'AMP and can be further transformed into other cellular metabolites, such as inosine through nucleotidases or alkaline phosphatase enzymes (Thorell *et al.*, 1996). 5'IMP levels show circadian patterns similar to those of 5'AMP and 5'GMP in human breast milk. However, 5'AMP concentrations peak at the end of the light period (Figure 32.5). Overall, the circadian rhythms of the concentrations of purines in breast milk were consistent with their role as sleep inducers.

32.2.2 Pyrimidines

Uridine 5'monophosphate

Uridine (Figure 32.2) is the major form of pyrimidine nucleosides taken up by the brain and it is phosphorylated to the nucleotide 5'UMP which has been also implicated in the sleep function. A previous study demonstrated a depressive effect of 5'UMP on the CNS and showed that administration of 5'UMP has sleep-promoting actions (Dobolyi e*t al.*, 2011).
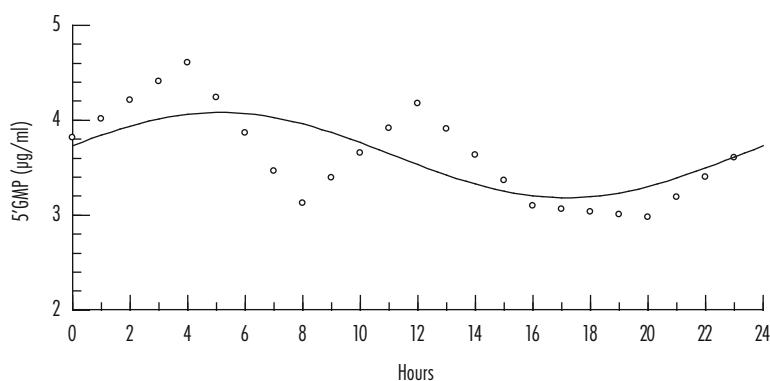
Figure 32.4. This graph depicts the fluctuations of guanosine 5'monophosphate levels (5'GMP) during 24-hrs. Circadian rhythm is shown by a sinusoidal curve (Sánchez *et al.*, 2009.
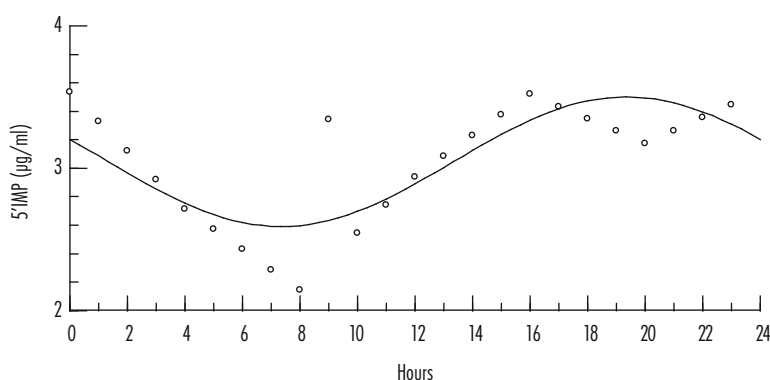
Figure 32.5. This graph depicts the fluctuations of inosine 5'monophosphate levels (5'IMP) during 24-hrs. Circadian rhythm is shown by a sinusoidal curve (Sánchez *et al.* 2009).Circadian rhythm is shown by a sinusoidal curve (Sánchez *et al.*, 2009.

Although a clear circadian rhythm of the 5'UMP levels in human breast milk was not found, a peak in concentration was seen during the night (Sánchez *et al.*, 2009). As had been demonstrated with 5'AMP, newborns who drank a 'night' artificial formula enriched with 5'AMP and 5'UMP, exhibited improved sleep (Figure 32.6) (Cubero *et al.*, 2006).

Cytidine 5'monophosphate

In contrast to what was found for 5'UMP, concentration of another pyrimidine, 5'CMP (Figure 32.2), showed a circadian rhythm in breast milk (Figure 32.7). 5'CMP levels exhibited a pattern with a peak during the day (light period). This diurnal rhythm suggests a complementary role of
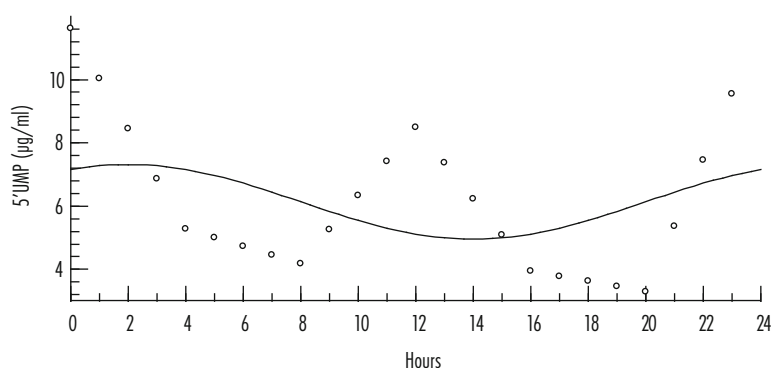
Figure 32.6. This graph depicts the fluctuations of uridine 5′monophosphate levels (5′UMP) during 24-hrs. Circadian rhythm is shown by a sinusoidal curve (Sánchez *et al.*, 2009).

5′CMP with the sleep-inducing effects of the purines and 5′UMP which improve the sleep/wake cycle (Sánchez *et al.*, 2009). Furthermore, based on the recent results of Bracken *et al.* (2011), the administration of this nucleotide on cocaine-dependent individuals had no effect on any of the sleep parameters measured, including sleep efficiency, sleep latency, total sleep time, etc.

Thymidine 5′monophosphate

Another pyrimidine, 5′TMP (Figure 32.2), has not shown any circadian rhythm, and unless a link between 5′TMP and sleep induction has not been demonstrated, 5′TMP does have a peak in concentration (Figure 32.8), suggesting a potential biological role of this pyrimidine nucleotide in sleep (Sánchez *et al.*, 2009).

32.3 Summary

Previous literature and the study of circadian rhythms in components of human breast milk, suggest that breast milk helps a newborn adjust the circadian pattern in harmony with his environment (day/night). Oscillations in the levels of sleep-inducing nucleotides with acrophase at night would naturally encourage sleep in infants (Table 32.1). The development of a circadian rhythm is crucial for the proper functioning and synchronization of all the systems in the human body (Cubero *et al.*, 2006; Sánchez *et al.*, 2009).'

Little information exists in the field of chronobiology in respect to breast milk. The chrononutrition 'boom' during recent years, as well as increasing the awareness of the importance of breastfeeding to newborn health, should encourage future research into the formation, composition, and biological effects of human breast milk.
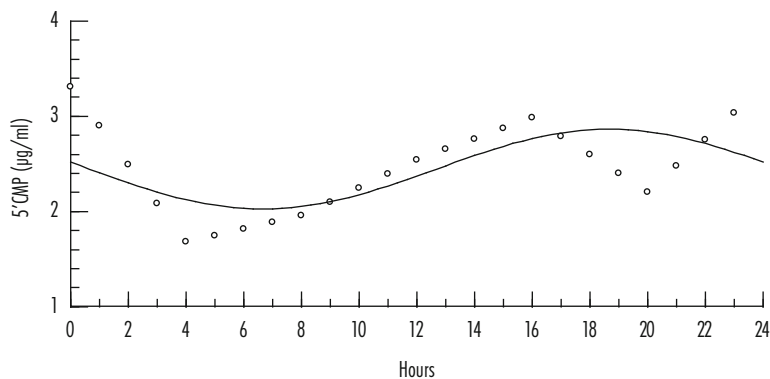
Figure 32.7. This graph depicts the fluctuations of cytidine 5'monophosphate levels (5'CMP) during 24-hrs. Circadian rhythm is shown by a sinusoidal curve (Sánchez *et al.*, 2009).
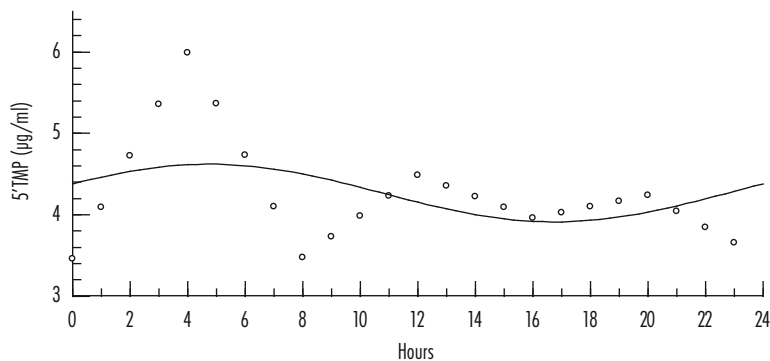
Figure 32.8. This graph depicts the fluctuations of thymidine 5'monophosphate levels (5'TMP) during 24-hrs. Circadian rhythm is shown by a sinusoidal curve (Sánchez *et al.*, 2009).

Table 32.1. Overview of how breast milk nucleotides are involved in sleep/awake function based on the data from bibliography.

Base	Nucleotide	Peak concentration (acrophase)	Rhythm	Sleep/awake induction
adenosine	adenosine 5-monophosphate (5'AMP)	night	circadian	sleep
guanosine	guanosine 5-monophosphate (5'GMP)	night	circadian	sleep
inosine	inosine 5-monophosphate (5'IMP)	day	circadian	awake
uridine	uridine 5-monophosphate (5'UMP)	night	N/A	sleep
cytidine	cytidine 5-monophosphate (5'CMP)	day	circadian	awake
thymidine	thymidine 5-monophosphate (5'TMP)	night	N/A	sleep

Future studies should be conducted with a greater number of participants to obtain more thorough knowledge of the synthesis and secretion of human breast milk. Because of the potential public health benefits, understanding the nature and function of the 'chrononutrients' in human milk, should be given a high priority within the field of pediatric research for the next decade.

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Summary points

- The breakfast tryptophan intake affects circadian typology and sleep habits for children and students aged 2-25 yrs.
- Breakfast tryptophan and vitamin B6 intakes and sunlight-exposure can promote morning-typology especially in young children aged 2-6 yrs.
- This review takes its results from questionnaire studies administered in a university soccer team of which the members were aged 18-25 yrs.
- Tryptophan intake effects can be eliminated by evening exposure to a fluorescent lamp.
- The salivary melatonin level of the soccer team members was suppressed by the exposure to lights from the fluorescent lamp.
- Evening typology correlated positively with body mass index (BMI) both of young children aged 2-6 yrs and their mothers.

33. Tryptophan and sleep: breakfast tryptophan content and sleep

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Abstract

The breakfast tryptophan intake affects circadian typology and sleep habits for children and students aged 2-25 yrs. Breakfast tryptophan and vitamin B6 intakes and sunlight-exposure can promote morning-typology in young children aged 2-6 yrs based on the results of questionnaire studies and in university soccer team members aged 18-25 yrs based on intervention studies. Tryptophan intake effects can be abolished by evening exposure to a fluorescent lamp; for example, salivary melatonin level of the soccer team members was suppressed by exposure to lights from fluorescent lamps. Evening typology correlated positively with body mass index both of young children aged 2-6 yrs and their mothers.

Keywords: breakfast-tryptophan, sleep habits, circadian typology, obesity, evening lighting

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Abbreviations

BMI	Body mass index
G1	Group 1
G2	Group 2
G3	Group 3
IA	Intervention A
IB	Intervention B
LWP	Last week period
M-E	Morningness-eveningness
SD	Standard deviation
Trp	Tryptophan

33.1 Introduction

That tryptophan taken from meals can be used for the synthesis of serotonin was first demonstrated by Gessa *et al.* (1974). They showed that the acute administration of a mixture of essential amino acids lacking tryptophan produced a specific and long-lasting reduction of brain tryptophan and serotonin levels in rats. Since then, the method of 'tryptophan free diets' has indirectly shown the anti-depressant effects of serotonin (Fedda, 2000; Moore *et al.*, 1998, 2000; Van der Does, 2001). The tryptophan depletion increased wake percentage and rapid eye movement sleep density (Carhart-Harris *et al.*, 2009; Moore *et al.*, 1998, 2000; Van der Does, 2001; Voderholzer *et al.*, 1998). In the psychiatric field, this method has shown that the treatment with selective serotonin reuptake inhibitors and bright light therapy could have anti-depressant effects via serotonin synthesis (Booij *et al.*, 2005; O'Reardon *et al.*, 2004) and tryptophan depletion can be used for the treatment of mania (Applebaum *et al.*, 2007).

There are many reports on the effects of supplements or foods containing high levels of tryptophan on sleep in humans. Heine *et al.* (1995) and Silber and Schmitt (2010) summarised the neurobehavioral effects of tryptophan supplements added to diets. Tryptophan-free diets induce depressed mood, insomnia, increased carbohydrate intake and disturbances in affective reaction control and sexual behaviour, whereas tryptophan-loaded diets promote elevated mood, calmness and drowsiness, decreased appetite for carbohydrates, decreased pain threshold, and memory improvements. Cauffield and Forbes (1999) reported that dietary supplements of tryptophan can be used for the treatment of depression, anxiety and sleep disorders. Sarwar (2001) reported that supplying the supplement as the powder and liquid concentrate forms of soy-based infant formulas resulted in significant increases in the concentration of tryptophan in the plasma and brain, and serotonin and 5-hydroxyindole-3-acetic acid in brain of 'rats' model for human compared to those fed un-supplemented formulas. Steinberg *et al.* (1992) measured the plasma tryptophan and sleep latency of human infants fed commercial formula containing high levels of tryptophan (882 µmol/l). These infants showed significantly higher plasma tryptophan:large

neutral amino acids ratios and also significantly shorter sleep latencies (18.7 min on average) than infants fed formulas containing less added tryptophan (27.7 min).

Cubero *et al.* (2005) reported that tryptophan in human breast milk showed a circadian rhythm with the peak at around 03:00 and this peak leads to the circadian peak of the 6-sulfatoxymelatonin (the metabolite of melatonin) excreted contents in urine of their babies at 06:00. This circadian peak also promoted nocturnal sleep. Cubero *et al.* (2007) also showed that tryptophan added to milk could improve sleep hours, sleep efficiency and sleep latency for the infants. This research group also reported that nutritionally enriched cereals including 225 mg tryptophan per 100 g of product improved sleep health (Cubero *et al.*, 2007). Heine *et al.* (1995) and Heine (2000) pointed out that human milk protein consists of 28% lactalbumin, whereas lactalbumin in cow's milk contributes to only 3% of total protein. And tryptophan supply from human breast milk is, consequently, much higher than from equinitrogenous amounts of cow's milk.

Garrido *et al.* (2009) reported that the consumption of a nutraceutical product twice a day made with Jerte Valley cherries significantly increased urinary 6-sulfatoxymelatonin and actual sleep time and immobility in human participants aged 20-75 yrs. They concluded that these effects were due to high concentrations of tryptophan contained in these cherries.

As for the effects of tryptophan in meals, the time of meals in human circadian rhythms has not been researched so far. Recently, the research group of Harada *et al.* has started exploring the breakfast tryptophan effects on circadian typology and sleep habits for children and students aged 2-25 yrs. The following sub-chapters introduce the results of their published and as yet unpublished research.

33.2 Breakfast tryptophan intake leading to morning-typed life in Japanese children and students aged 1-15 yrs

Tryptophan can be metabolised via 5-hydroxytryptamine, serotonin to melatonin by a series of 4 enzymes in the pineal body (Stehle *et al.*, 2011). Lack of serotonin in body fluid in the brain during daytime can trigger several psychiatric disorders, for example seasonal affective disorder (Heine *et al.*, 1995), while shortage of plasma-melatonin at night can be related to sleep disorders (Kondo and Wakamura, 2011). The Torsvall-Åkerstedt Diurnal type scale (1980) and the original questionnaire including questions on sleep habits (Nakade *et al.*, 2009), mental symptoms (Krejci *et al.*, 2011; Nakade *et al.*, 2009), and contents of meals were administered to 1,055 infants aged 0-6 yrs, 751 students attending an elementary school, and 473 students attending junior high school in Kochi City (33°N). The index of tryptophan taken at breakfast (Trp-Index) was calculated as tryptophan amount per one meal based on the tryptophan included in each 100 g of the foods and a standard amount of food per one meal. A significant positive-correlation between M-E scores and Trp-Index was not shown by relatively older students, aged 9-15 yrs (Pearson's test, r=0.044-0.123, P=0.071-0.505), whereas a significant positive correlation was shown by infants and young elementary school students aged 0-8 yrs (r=0.180, 0.258, P=0.001). Index of tryptophan taken at

breakfast by morning-typed infants was much higher than that by evening-typed ones (Kruskal-Wallis test, df=2, χ^2-value=18.51, P<0.001), whereas the index at supper by morning-typed infants was similar to that by evening-type infants (df=2, χ^2-value=2.05, P=0.358) (Figure 33.1).

The more frequently the infants had difficulty falling asleep at bedtime and waking up in the morning, the lower the Trp-Indices taken at breakfast (Kruskall-Wallis-test, P=0.027 for difficulty falling asleep; P=0.008 for difficulty waking up). The longer the sleep latency of the infants was, the lower the Trp-Index (Figure 33.2) (Kruskall-Wallis-test, df=5, χ^2-value=14.72, P=0.011). The more frequently infants became angry due even to a minor trigger (Kruskal-Wallis test: χ^2-value=18.43, df=3, P=0.001), or depressed (Kruskal-Wallis test: χ^2-value=15.72, df=3, P=0.001), the lower (more evening-typed) the M-E scores were. Tryptophan ingested at breakfast might be important for helping children to maintain a morning-type diurnal rhythm, high quality of sleep, and good mental health through the metabolism of tryptophan to serotonin in daytime and further to melatonin at night.

33.3 Integrated effect of tryptophan intake at breakfast and morning exposure to sunlight

Tryptophan intake at breakfast promotes morning-typed circadian typology and high sleep quality in Japanese children aged 0-6 yrs (Harada *et al.*, 2007). This effect might be accelerated by the morning exposure to sunlight. However, this has not yet been tested. A study was performed
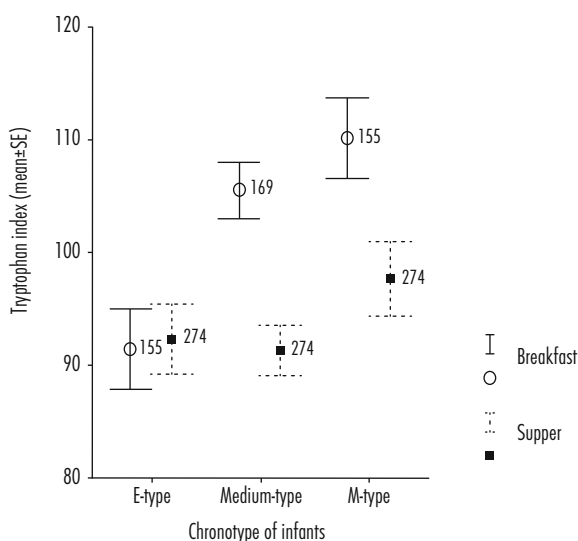
Figure 33.1. Tryptophan index shown by M-type much higher than that by E-type only in breakfast for Japanese infants aged 2-6 years.
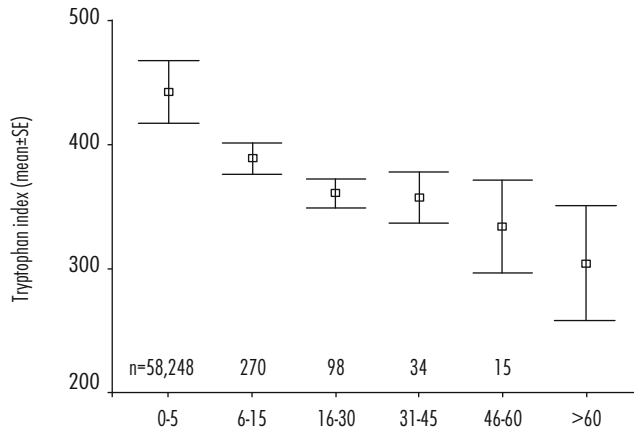
Figure 33.2. Relationship between sleep latency (min) and tryptophan index taken at breakfast in Japanese infants (Harada *et al.,* 2007).

to investigate the effect of sunlight exposure in Japanese children. In May 2006, a revised version of the integrated questionnaire (Harada *et al.*, 2007) was administered to 0-6 yr old children attending one of 12 kindergartens. A total of 906 parents answered the questionnaire for their children and themselves (response rate: 67.4%). The integrated questionnaire included the revised version for children of the Torsvall-Åkerstedt Diurnal type scale (1980) Questionnaire and questions on sleep, nutritional balance, mental health, and sunlight exposure. Analysis was made on data from 744 children aged 2–6 (385 girls, 359 boys) whose average value of the diurnal type scale score was 20.6 (SD=±3.46).

Children who had breakfast at regular times were less frequently angry (χ^2-test: χ^2-value=18.30, df=6, *P*=0.006) and depressed (χ^2-test: χ^2-value=12.75, df=2, *P*=0.002). Children who took nutritionally well-balanced breakfasts tended to be more morning-typed (χ^2 value=30.55, df=3, *P*<0.001), and woke up earlier (χ^2 value=17.15, df=3, *P*<0.001), went to bed earlier and fell asleep at earlier times (χ^2 value=24.80, df=3, *P*<0.001). Children who took one or more main-dish (es) (fish, meat, beans, eggs, etc.) with sunlight exposure of more than 30 min after breakfast were more morning-typed (Mann-Whitney U-test: z=-2.293, *P*=0.022) and showed earlier bedtime in weekdays (Mann-Whitney U-test: z=-1.910, *P*=0.056, Figure 33.3) and shorter difference in wake-up time between weekdays and weekend (Mann-Whitney U-test: z=-3,719, *P*<0.001, Figure 33.4) than those with less than 30 min, while there were no significant morning-type-driving effects of the sunlight exposure for the children taking breakfast including no main dish (Mann-Whitney U-test: Diurnal type scale scores, z=-0.098, *P*=0.922; bedtime: z=-0.630, *P*=0.529; wake-up-time difference: z=-0.939, *P*=0.348).

Breakfast containing a good balance of nutrition might be a strong *zeitgeber* for circadian oscillators in children. The morning-type-driving effect of protein intake via tryptophan-to-serotonin-synthesis could be accelerated by morning exposure to sunlight after taking breakfast.
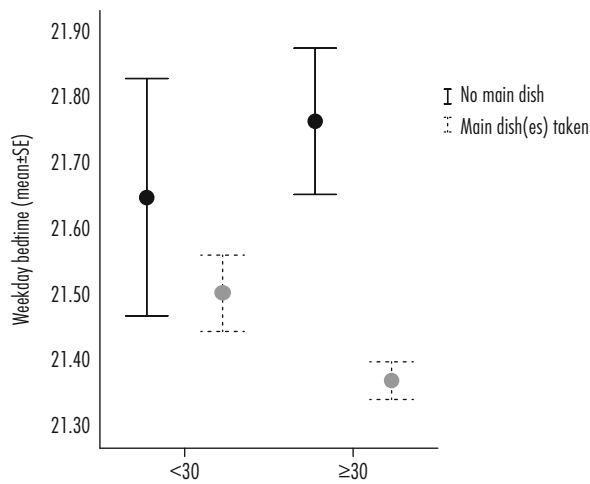
Figure 33.3. Effect of sunlight exposure on bedtime in relation to whether the infants eat food containing a protein resource (e.g. fish, meat, soy-food, cheese, etc.) (Nakade *et al.,* 2009).
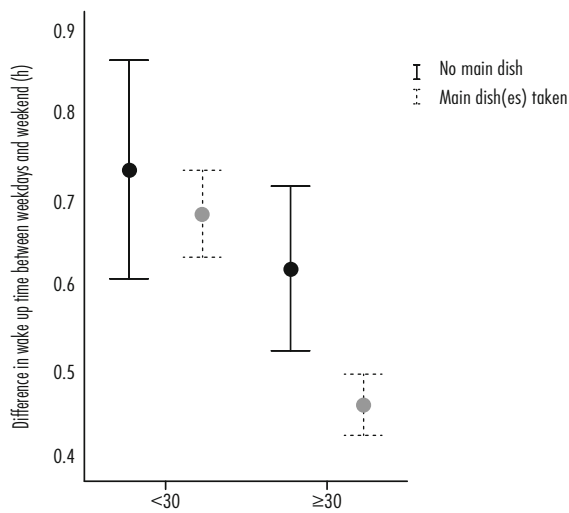
Figure 33.4. Effect of sunlight exposure on difference in wake-up time between weekdays and weekend in relation to whether the infants eat food containing a protein resource (e.g. fish, meat, soy-food, cheese, etc.) (Nakade *et al.,* 2009).

33.4 Breakfast tryptophan and vitamin B6 intake and morning exposure to sunlight and morning-typology in young children

From an epidemiological and physiologic anthropological (Japanese culture on breakfast) point of view, the integrated effects of the amount of tryptophan and vitamin B6 intake and the following exposure to sunlight on the circadian typology and sleep habits in Japanese young children aged 2-6 years were examined using the revised version of the calculating system of tryptophan (Tryptophan-index 2009) and vitamin B6 intake (Vitamin-B6 index 2009) at breakfast. The positive and significant correlation was shown between the Diurnal type scale score Torsvall and Åkerstedt (1980) constructed and Tryptophan-index and also Vitamin B6 intake index (Pearson's correlation test: when infants were exposed to sunlight for less than 10 min after breakfast, r=0.271, n=217, $P<0.001$; when they were exposed for more than 10 min, r=0.320, n=303, $P<0.001$) (Figure 33.5). This positive correlation between M-E score and amount of Trp intake was shown only in children who were exposed to sunlight for longer than 10 min after breakfast (Pearson's correlation test, exposed less than 10 min: r=0.174, n=100, $P=0.082$; exposed more than 10 min: r=0.333, n=70, $P=0.005$).

These results might support the following hypothesis: higher tryptophan and vitamin B6 intake at breakfast could promote the synthesis of serotonin via light stimulation in the morning in infants.
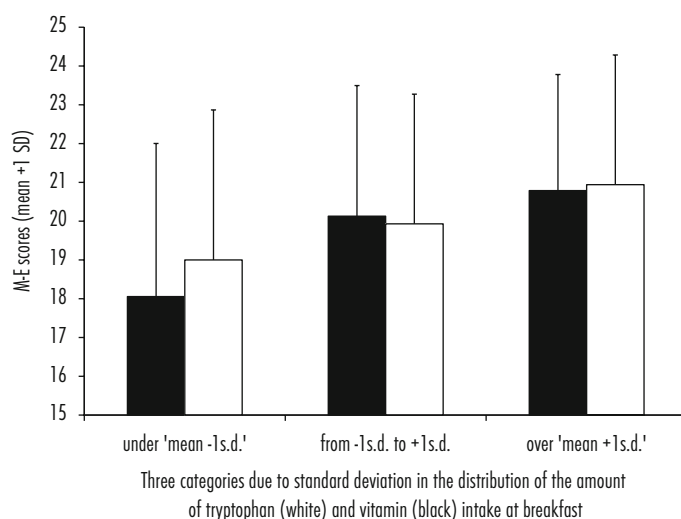
Figure 33.5. Tryptophan (white column) and vitamin B6 (black column) intake at breakfast and Diurnal type scale (M-E) scores in Japanese infants aged 2-6 yrs (Kruskal-Wallis-test: tryptophan, χ^2-value=2.592, df=2, $P=0.274$; Vitamin-B6,χ^2-value=6.177, df=2, $P=0.046$) (Nakade et al., 2012).

33.5 Integrated intervention in breakfast and subsequent sunlight exposure and morning-typed diurnal rhythms

Whether an intervention such as the consumption of tryptophan and vitamin B6 at breakfast, followed by sunlight exposure could effectively increase the circadian typology of the participants of Japanese University sport club members was examined with an intervention epidemiological method. The students were divided evenly into three groups with equal numbers of the different chrono-types to eliminate bias.

Participants in G1 received no intervention. Participants in G2 were asked to eat protein resources such as fermented soybeans and Vitamin B6 resources such as bananas at breakfast and were also asked to record their breakfast. Participants in G3 were asked to do the same as G2 and also to expose themselves to sunlight after breakfast and record the duration of exposure.

Based on the paired individual comparison (Wilcoxon test) before and after the intervention, participants of G3 showed significant advances in sleep quality (Figure 33.6) and regularity in life-time schedule (Figure 33.7). Evening-typed participants who made up 50% of all participants just before the intervention in G2 and G3 significantly shifted to more morning-typed afterwards (Wilcoxon signed-ranks test: G1, evening-typed: P=0.60, G1, morning-typed: P=0.89, G2 and G3, evening-typed: P=0.03, G2 and G3, morning-typed: P=0.14). For the evening-typed 50% of all participants in G2 and G3, a significant and positive correlation was shown between the
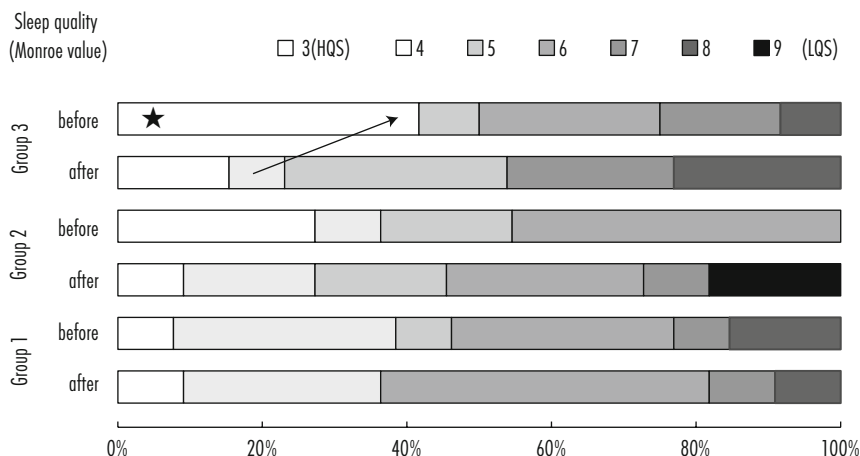
Figure 33.6. Effects of one-month intervention program on the quality of sleep (Monroe score) in Japanese University sport team members, all males aged 18-25 yrs (Takeuchi *et al.*, in press).

G1: no intervention, G2: breakfast contents (fermented soy-beans and banana), G: breakfast contents (fermented soy-beans and banana) and sunlight exposure after breakfast. LQS: Low quality of sleep; HQS: High quality of sleep; Before: Before the intervention; After: After the intervention. ★: P<0.05, Wilcoxon test.
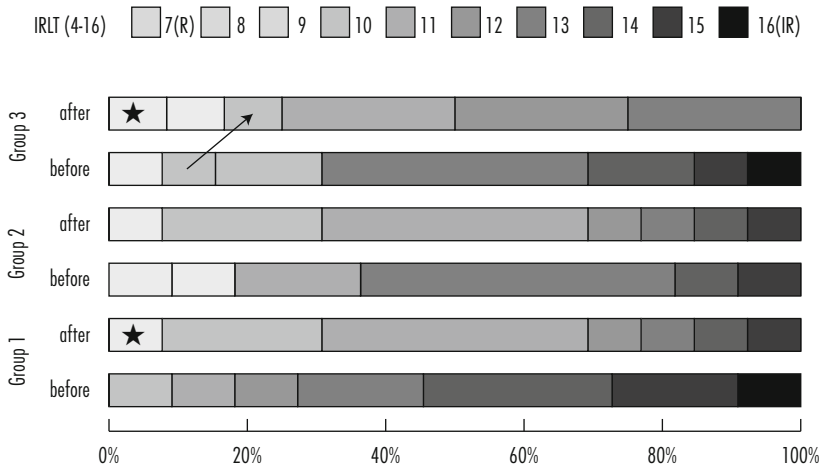
Figure 33.7. Effects of one-month intervention program on the regularity in life episodes among Japanese University sport team members, all males aged 18-25 yrs (Takeuchi *et al.,* in press).
G1: no intervention, G2: breakfast contents (fermented soy-beans and banana), G: breakfast contents (fermented soy-beans and banana) and sunlight exposure after taking breakfast. IRLT: Index of irregularity of life time; IR: irregular: R: regular; ★: *P*<0.05, Wilcoxon test.

change in Trp amount consumed at breakfast and the change in M-E score before and after intervention (Pearson's correlation test: r=0.612, *P*=0.020).

Based on the correlation analysis, it might be hypothesised that the consumption of Trp at breakfast causes a shift in the circadian typology of University students to more morning-typed.

33.6 Tryptophan intake effects can be abolished by evening exposure to fluorescent lamp

The effects of incandescent light exposure at night during a one-month intervention. The effects of intervention on sleep-wake cycle and mental health condition were estimated by asking Japanese university students to eat foods including protein, vitamin B6 at breakfast and to be exposed to sunlight thereafter (October-November, 2008, IA; Takeuchi *et al.,* in press; Wada *et al.,* 2010), as well as being exposed to incandescent lights ('low temperature' light) at night (October-November, 2010, IB).

Eighty-three (2008) and 94 (2010) male team members of a university soccer club were divided into 3 groups (IA-G1, IB-G1: no intervention; IA-G2: asking them to eat protein resources like as fermented soybeans and VB6 resources like banana at breakfast; IA-G3, IB-G2: same as for IA-G2 plus sunlight exposure after breakfast; IB-G3: same as for IB-G2 plus incandescent light exposure at night). The participants kept a sleep diary throughout the 30-day intervention period

which was divided into 3 periods (first week period, medium period of 16 days, last week period). Salivary melatonin was measured around 23:00 at mid-point and just after 1 month period of IB.

Participants of IA-3 showed phase advancement within 4 weeks of intervention. In the IB, 3 phase points of bed time, falling asleep time and the middle of sleep hours were significantly earlier (Mann-Whitney U-test: z=-2.309~-6.547, $P<0.001$) than those in the IA. In IB-G3, the longer they spent under incandescent lights at night, the significantly higher the frequency to feel their sleep deep (Pearson's correlation test: r=0.515, $P=0.034$) in LWP. The concentration of salivary melatonin of IB-G3 was significantly higher than that of IB-G1, IB-G2 both at midday and the day just after the IB (Kruskal-Wallis-test: χ^2-value=8.0, df=2, $P=0.018$), whereas there were no significant differences on the day just before the IB (χ^2-value=0.96, df=2, $P=0.63$). Participants of IB-G3 implemented the contents of morning intervention (breakfast and light exposure) on more days than those of IB-G2 (Mann-Whitney U-test medium period of 16 days: z=-2.718, $P=0.006$, LWP: z=-3.000, $P=0.003$).

The effect of the IA seems to last for 2 years till IB. Shifting to morning-type in IB-G3 might be led back to better implementation of the morning intervention (taking protein-rich dish(es) at breakfast and following exposure to sunlight). The integrative intervention in breakfast, morning light exposure and also evening light exposure seems to be significant in helping students as well as athletes to get better sleep and lead a morning-typed life.

33.7 **Morningness-eveningness and body mass index**

An epidemiological study on the relationship between circadian typology and BMI of Japanese mothers aged 20-40 yrs and circadian typology of their young children aged 2-6 yrs.

There are currently serious problems of increasing obesity in developed countries and many children who sleep less have been reported to be obese. However, there have been no studies on the relationship between mothers' BMI and the circadian typology of their young children aged 2-6 yrs. Such a relationship was examined among Japanese young children and their mothers from an epidemiological point of view.

An integrated questionnaire (including the Torsvall-Åkerstedt Diurnal type scale (1980) on diurnal rhythm, sleep habit, meal habit, light condition at night, and weight & height was administered to the parents and their children aged 2-6 yrs, and about 62% of 863 mothers answered it for themselves and their children. Software for PC (12.0J for windows; SPSS Inc., Chicago, IL, USA) was used for statistical analysis of the questionnaire data.

All the obese mothers scoring higher than 28 for BMI had Torsvall-Åkerstedt Diurnal type scale scores less than 18 and were more evening-typed than those scoring less than 28 (Mann-Whitney U-test: z=-3.024, $P=0.02$) (Figure 33.8). A higher ratio of the obese mothers with BMI>28 watched TV later than 23:00 (χ^2-test: χ^2-value=3.87, df=1, $P=0.049$) and used fluorescent lamps while
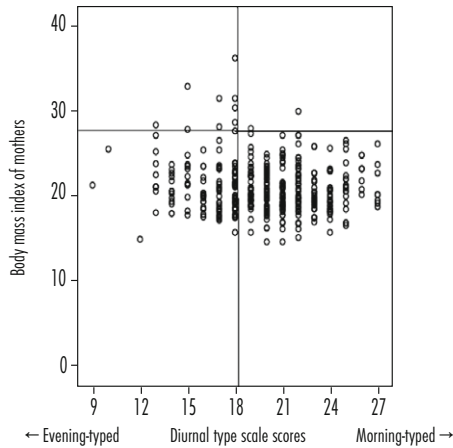
Figure 33.8. Correlation between body mass index and the diurnal type scale scores in the parents (mostly mothers) of Japanese infants aged 1-6 yrs (n=404, 2009).

watching TV later than 23:00 (χ^2-value=5.20, df=1, P=0.023) than that of the other mothers with a BMI<28. The obese mothers showed a higher frequency of depression (χ^2-test: χ^2-value=8.08, df=3, P=0.044) and were more likely to be irritated (χ^2-test: χ^2-value=6.44, df=3, P=0.09) than non-obese mothers. The children of the obese mothers scoring over 28 were significantly more evening-typed (mean±SD=18.5±3.6) than those (21.1±3.2) of the other mothers (Mann-Whitney U-test: z=-2.36, P=0.018).

These results might imply that mothers watching midnight TV under fluorescent lamps have an evening-typed life, eating foods at night which may easily lead to obesity and their young children have the opportunity to adopt the same evening-typed life of their mothers.

33.8 Comparative studies between Czech and Japanese infants on circadian typology, breakfast habit and obesity

The circadian typology, breakfast habit and obesity based on BMI were compared between Czech and Japanese infants aged 5-6 yrs from an epidemiological point of view.

An integrated questionnaire was given to Czech (Ceske Budejovice at 49°N in Dec 2010-Feb 2011) and Japanese (Kochi at 33°N in June 2010) infants attending Kindergartens and nursery schools (80-90% response rate). The parents (>95% mothers) of these 79 Czech and 263 Japanese infants answered the questionnaires. The questionnaire included the Torsvall-Åkerstedt Diurnal type scale (1980), questions on breakfast habit (regularity of timing and contents), sleep habit, height and weight. Obesity was judged based on BMI and the evaluation figure for infants compiled by WHO (2007).

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A higher percentage of Czech infants (20.6%) were obese than Japanese infants (2.3%) (χ^2-test, χ^2-value=32.9, df=3, P<0.001). Although Czech infants showed on average higher M-E scores of 22.6 (±2.9: SD) than Japanese ones (21.0±3.1) (Mann-Whitney U-test: z=-4.4, P<0.001), obese Czech infants were more evening-typed (mean ± SD of M-E: 19.7±2.9) than non-obese ones (23.1-23.4, ±1.0-2.9) (Kruskal-Wallis test: χ^2-value=17.8, df=3, P<0.001) whereas there was no such difference in Japanese infants (χ^2-value=2.0, df=3, P=0.57). A clear link between an evening-typed life and obesity was shown by Czech infants in the winter season (Table 33.1, 33.2).

Infants who ate breakfast at a regular time everyday were more morning-typed than those who did it less than 4-5 times per week in both countries (Kruskal-Wallis test: χ^2-value=8.3-38.9, df=2, P=0.016 or <0.001). Japanese infants who ate sweet foodstuffs rarely or never were more morning-typed than those who did so more than 1-2 times (Kruskal-Wallis test: χ^2-value=14.4, df=3, P=0.002 [Japanese], χ^2-value=3.3, df=3, P=0.35 [Czech]).

Taking breakfast at a regular time could become a *zeitgeber* for Czech and Japanese infants. A high percentage of obese infants only on the Czech side and their evening-typed life might be related to the high latitude and winter season, which means that Czech infants have little or no exposure to morning sunlight as an important *zeitgeber* in winter.

33.9 Conclusion

Tryptophan intake at breakfast might be very important for good sleep because of the underlying mechanism of promoting quality sleep, including triggering the onset of sleep due to high amount of plasma melatonin synthesised from serotonin in the pineal which is synthesised again in the pineal in the daytime especially several hours after the breakfast.

Table 33.1. Comparative analysis on the relationship between obesity and diurnal scale scores (ME score) and sleep habits between infants from the Czech Republic and from Japan.

		Percentage of BMI-for-age (based on WHO database)				Kruscal-Wallis text (df=3)	
		under 50%	under 75%	under 95%	over 95% (obesity)	χ^2	P
Czech	(mean)	23.2	23.1	23.4	19.7*	17.8	0.000
	(s.d.)	2.88	0.99	1.19	2.91*		
Japan	(mean)	20.8	21.0	21.6	22.0	2	0.567
	(s.d.)	3.18	3.16	3.13	3.46		

*Values were significantly different.

Table 33.2. Comparison of circadian typology, sleep habits and lunch timing between obese and not obese young Czech and Japanese children.

		Accumulated ME score	GP score	Weekdays awake time	Holidays awake time	Holidays sleep time	Lunch time (holidays)
Czech Republic							
Not obese	mean	23.2	4.3	6.2	6.7	9.9	11.6
(under 95%, n=58)	s.d.	2.5	1.6	0.6	0.8	1.1	1.6
Obesity	mean	19.7	5.7	6.5	7.5	10.8	12.3
(over 95%, n=15)	s.d.	2.9	1.6	0.5	0.3	0.7	0.4
U-test	z	-4.2	-2.97	-1.50	-3.71	-2.74	-3.74
	P	>0.001*	0.003*	0.133	>0.001*	0.006	>0.001*
Japan							
Not obese	mean	21.0	4.4	7.0	7.5	9.7	12.2
(under 95%, n=210)	s.d.	3.2	1.5	0.6	0.8	0.8	0.5
Obesity	mean	22.0	5.5	7.8	8.2	10.3	12.1
(over 95%, n=5)	s.d.	3.5	2.1	0.8	1.2	0.5	0.5
U-test	z	-0.68	-1.24	-2.09	-1.33	-1.72	-0.22
	P	0.496	0.216	0.037*	0.185	0.085	0.828

*Values were significantly different with $P<0.05$.

In Japanese society, a big problem is that the preference for 'fluorescent lamps' as lighting between sunset and bedtime depresses the melatonin level (Harada, 2004; Kondo and Wakamura, 2011). The combined intervention of eating breakfast containing high protein foods such as fish, meat, ham, egg and fermented soy-beans, etc. and using lighting that emits low temperature ('orange' coloured) may help Japanese people to get better quality sleep. In the case of people living in high latitude areas, taking tryptophan at breakfast is important not only for better sleep at night but also for preventing seasonal affective disorders (depression in winter season due to low amount of serotonin) (Molnar *et al.,* 2010).

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